Patient Adherence to Chronic Gout Medication

by

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Abstract

Background: Gout is the most common inflammatory arthritis in the U.S., with a prevalence of about 3.9%, or 8.3 million individuals. Gout is associated with significant morbidity, functional limitation and poor health-related quality of life. In addition, gout has a significant impact on economic burden for the U.S. healthcare system (total annual direct medical cost is about $4 billion). Although the effective treatments are available and the treatment guidelines show the clear treatment pathways, the patient adherence to chronic gout treatments is known to be low compared with other chronic diseases. Most previous studies have been based on relatively small patient populations, so their results are difficult to generalize to the whole U.S. population.

Objectives: The objectives of this project are to describe and examine factors associated with the long-term medication adherence of gout patients in a large sample of the U.S. population.

Methods: This is a retrospective cohort study using the GE centricity electronic medical record (EMR) database. The age, sex and race/ethnics distributions for the data are generally similar to that of the overall U.S. population. The primary outcome is patient adherence measured by the Medication Possession Ratio (MPR), which is used widely to measure medication adherence for chronic disease(s). In addition to adherence measured by the MPR, persistence was studied as the second outcome; because the MPR is calculated by the proportion of days during the follow-up period in which a patient has available medications, it is difficult to capture the patient's behavior. To understand patient behavior better, persistence was analyzed in addition to adherence measured by the MPR.

Results: The total sample size for this study is 91,629 patients. The sample size of this study is much larger than those of previous studies. The unadjusted adherence for the whole study sample

was 46.4%. In the adjusted adherence analysis, all 19 covariates (type of medication of Urate-lowering therapy (ULT), age, gender, race, region, insurance, index year, BMI, CKD stage, specialist vs. non-specialist provider classifications, a diagnosis of tophi, a diagnosis of renal impairment, serum uric acid measurements (sUA), number of diagnoses of acute gout, comorbidities (Charlson Comorbidity Index), the use of NSAIDs, colchicine, or glucocorticoids, and heath care utilization) produced statistically significant parameter estimates. The type of medication (Febuxostat or Allopurinol) of ULT had the most significant impact on adherence. In the unadjusted persistence analysis, 34.8% of patients had a gap between prescriptions that qualified as non-persistence. The median time to non-persistence was 1.468 years. In the adjusted persistence analysis, 12 of the 19 covariates were statistically significant.

Conclusions: Type of medication (Febuxostat or Allopurinol) of ULT was one of the most critical factors for patient adherence to chronic gout medication. Because Febuxostat is a brand medicine whereas Allopurinol is a generic, there is a significant price difference between them, which may explain the lower adherence among patients on Febuxostat. Another reason why Febuxostat had lower adherence, may be that the treatment induced flares occurred more often for those on Febuxostat and patients did not understand the mechanisms inducing the flares at the process of ULT. However, because switching between medications cannot be analyzed in this study, further study to consider patients' behavior after switching medicines is needed to reach better conclusions regarding the impact of medications on adherence. From the study results and the analysis based on the conceptual framework for gout management, 3 possible areas are identified for future interventions to improve the adherence: 1) Cost burden mitigation (especially for brand medicine), 2) patient education and reminder systems, and 3) physician education.

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List of Acronyms/Abbreviations

ACR	The American College of Rheumatology
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CCHIT	The Certification Commission for Health Information Technology
CCI	The Charlson Comorbidity Index
CDS	Clinical Data Services
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
CVD	Cardiovascular disease
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
F/U	Follow-up
GP	General Practitioner
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	The International Statistical Classification of Diseases and Related Health Problems
IRB	Institutional Review Board
ISPOR	The International Society for Pharmacoeconomics and Outcomes Research
MPR	Medication Possession Ratio
NAMCS	The National Ambulatory Medical Care Survey
NHANES	U.S. National Health and Nutrition Examination Survey
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OR	Odds Ratio
PCPs	Primary Care Physicians
QOL	Quality of life
SES	Socioeconomic status
SF-36	Short Form-36
sUA	serum Uric Acid
ULT	Urate-lowering therapy
XOI	Xanthine Oxidase Inhibitor

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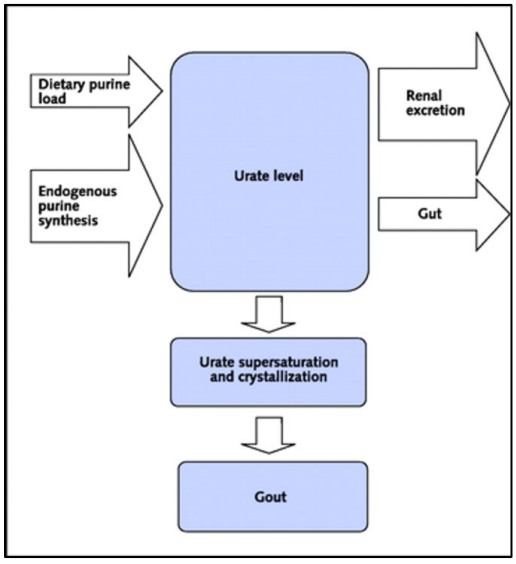
Chapter 1. Introduction/Background

Etiology and Pathology of Gout

Gout is the common arthritic condition caused by high serum uric acid (sUA) levels, in which monosodium urate crystals deposition forms in the joint space, leading to inflammation and swelling. [1]

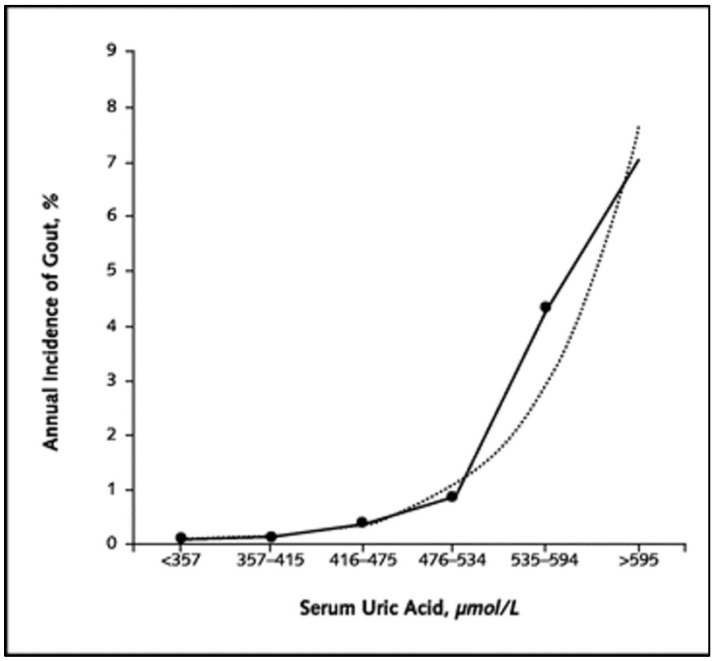
As Figure 1 shows, gout is mediated by the supersaturation and crystallization of uric acid within the joints. The amount of urate in the body depends on the balance between dietary intake, synthesis, and excretion. Hyperuricemia results from the overproduction of urate (10%), from underexcretion of urate (90%), or often a combination of the two. Approximately one third of urate elimination in humans occurs in the gastrointestinal tract, with the remainder excreted in the urine. [2]

Figure 1. Overview of the pathogenesis of gout. [2]



Previous studies have indicated a direct positive association between serum urate levels and a future risk for gout. [3] [4] The annual incidence of gout was less than 0.1% for men with serum uric acid levels less than 416 µmol/L, 0.4% for men with levels of 416 - 475 µmol/L, 0.8% for men with levels of 476 - 534 µmol/L, 4.3% for men with levels of 535 - 594 µmol/L, and 7.0% for men with levels greater than 595 µmol/L. In Figure 2, the solid line denotes these data points; the dotted line shows an exponential projection of the data points. [2]

Figure 2. The relationship between serum uric acid levels and the incidence of gout [2]



Epidemiology and Burden of Gout in the U.S.

A study based on the U.S. National Health and Nutrition Examination Survey (NHANES) conducted in 2007-2008 found that approximately 8.3 million people (including 6.1 million men and 2.2 million women) of the U.S. population had self-reported gout. The prevalence among

U.S. adults was 3.9%, the prevalence among men was 5.9% and the prevalence for women was 2.0%. The prevalence of gout increased with age, with the lowest prevalence (0.4%) in individuals ages 20–29 years and the highest prevalence (12.6%) among those ages 80 years or older. [5]

Table 1. Prevalence of gout and number of affected adults in the US, NHANES 2007–2008 [5]

	Prevalence, % (95% CI)	No. of affected US adults, million
Overall	3.9 (3.3, 4.4)	8.3
Sex		
Male	5.9 (4.7, 7.1)	6.1
Female	2.0 (1.5, 2.5)	2.2
Race/ethnicity		
White	4.0 (3.3, 4.8)	6.0
African American	5.0 (3.3, 6.6)	1.2
Mexican American	1.5 (1.0, 2.0)	0.3
Other	3.4 (1.2, 5.6)	0.8
Age category, years		
20–29	0.4 (0.0, 0.9)	0.2
30–39	1.3 (0.5, 2.0)	0.5
40–49	3.3 (1.8, 4.9)	1.5
50–59	3.7 (3.0, 4.4)	1.5
60–69	8.0 (5.8, 10.3)	2.0
70–79	9.3 (6.5, 12.0)	1.5
80+	12.6 (10.1, 15.1)	1.2

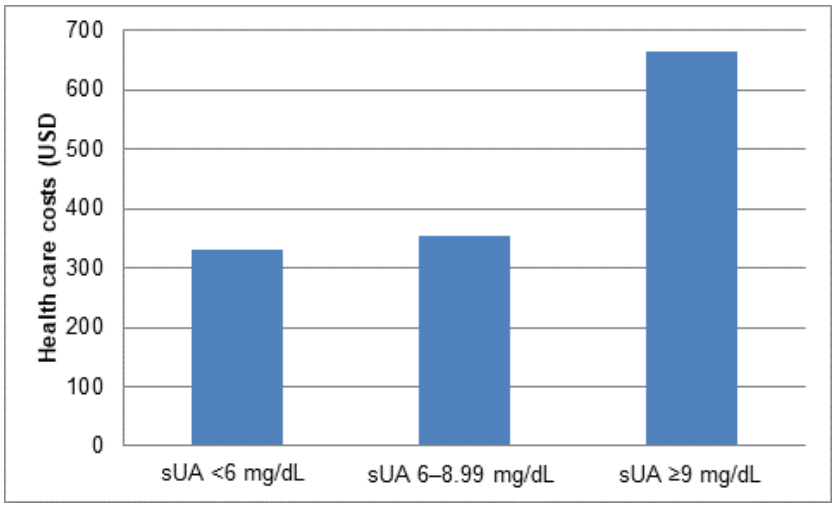
* The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2007–2008, with incorporation of sample weights. 95% CI = 95% confidence interval.

Gout is associated with significant morbidity, functional limitation and health-related quality of life (HRQOL) deficits. [6] [7] [8] Lee et al. assessed the impact of gout on HRQOL with the Short Form-36 (SF-36) and they found that the gout patients had significantly lower HRQOL than the matched general population without gout, for both the Physical Component Summary (PCS) and Mental Component Summary (MCS) ($P<0.002$ and $P<0.001$, respectively). [8]

Gout is associated with increased risk for cardiovascular morbidity and mortality. [9] [10] [11] Regarding the relationship between hyperuricemia/gout and AMI, Krishnan et al. reported that hyperuricemia was associated with a higher risk of acute MI (OR 1.11 [95% CI 1.08–1.15], $P < 0.001$) and that gout was associated with a higher risk of acute MI (OR 1.26 [95% CI 1.14–1.40], $P < 0.001$). [9] Also, concerning gout and coronary heart disease (CHD), Choi et al reported the multivariate relative risks among men with history of gout were 1.28 (95% confidence interval [CI], 1.15 to 1.41) for total mortality, 1.38 (95% CI, 1.15 to 1.66) for CVD deaths, and 1.55 (95% CI, 1.24 to 1.93) for fatal CHD, compared with men without history of gout and CHD at baseline. [10] Krishnan et al. also reported that gout is associated with increased risk for clinical heart failure, subclinical measures of systolic dysfunction and mortality. Among their studies, the patients with gout had greater mortality than those without (adjusted HR 1.58, 95% CI 1.40 to 1.78). [11]

In addition to clinical impacts, gout is also associated with a substantial economic burden in the U.S. (total annual direct medical costs of about $4 billion), and gout patients with poorly controlled sUA levels incur on average higher health care costs than patients whose sUA is better controlled. [12] [13] Park et al. reported that gout patients with high levels of sUA had higher gout-related health care costs; Mean adjusted gout-related health care costs were $332, $353, and $663, respectively for patients with lower, medium and higher sUA levels ($P < 0.05$). [12]

Figure 3. Adjusted gout-related health care costs for the 1-year post-index period [12]



Management of Gout: Chronic Phase and Acute Phase

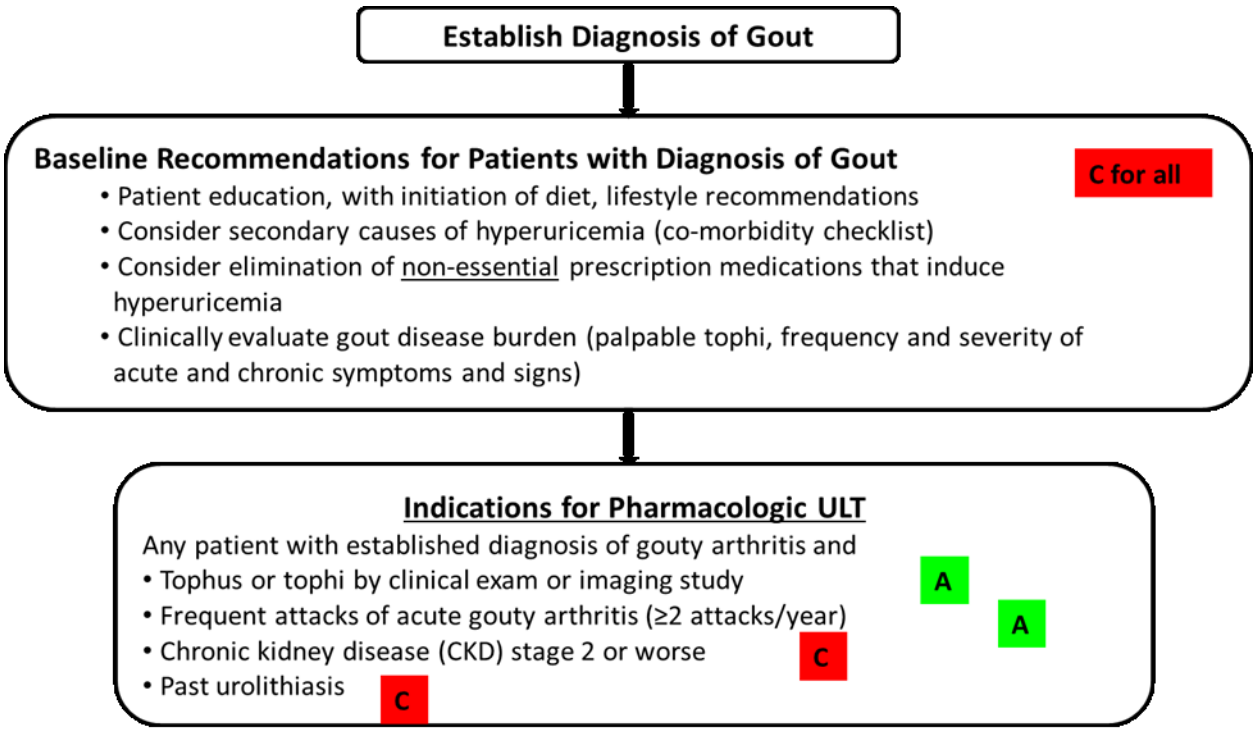
The optimal treatment of gout consists of: 1) adequate chronic use of urate-lowering therapies (ULT) aiming to achieve target sUA levels; and 2) anti-inflammatory therapies for acute flares and anti-inflammatory prophylaxis during the initial phase of ULT. [14] [15]

The American College of Rheumatology (ACR) guidelines recommend a comprehensive treatment strategy for management of gout. [Fig 4] At the acute phase with gout flares, treatment pharmacologic therapy (NSAIDs, corticosteroids, or colchicine) is recommended to remove pain. [Fig 5] Then, for gout attack prophylaxis, it is recommended to initiate low-dose colchicine or low-dose NSAIDs when initiating urate-lowering therapy (ULT). Anti-inflammatory prophylaxis should be continued from initiation of ULT for the greater of 1) a least 6 months, or 2) following achievement of the target serum urate, for 3 months in patients without or 6 months in patients with tophi on physical exam. [15] When initiating first-line ULT, Febuxostat or Allopurinol is

used, or if at least one of these is contraindicated or not tolerated, Probenecid can be used to treat to the sUA target of <6 mg/dL. sUA should be monitored regularly (every 2-5 weeks) during ULT titration, then every 6 months once the target sUA is achieved. [14]

Adequate lowering of the serum urate (sUA) to a target level of <6.0 mg/dl is associated with lower risk of acute flares and better function and quality of life. Thus, achievement of a target sUA <6.0 mg/dl with adequate long-term use of ULT is key to quality management of gout.

Figure 4. American College of Rheumatology Gout Guidelines: Recommendations and Overall Strategic Plan for Patients with Gout (see bottom of Figure for A, B, and C grading criteria) [14]



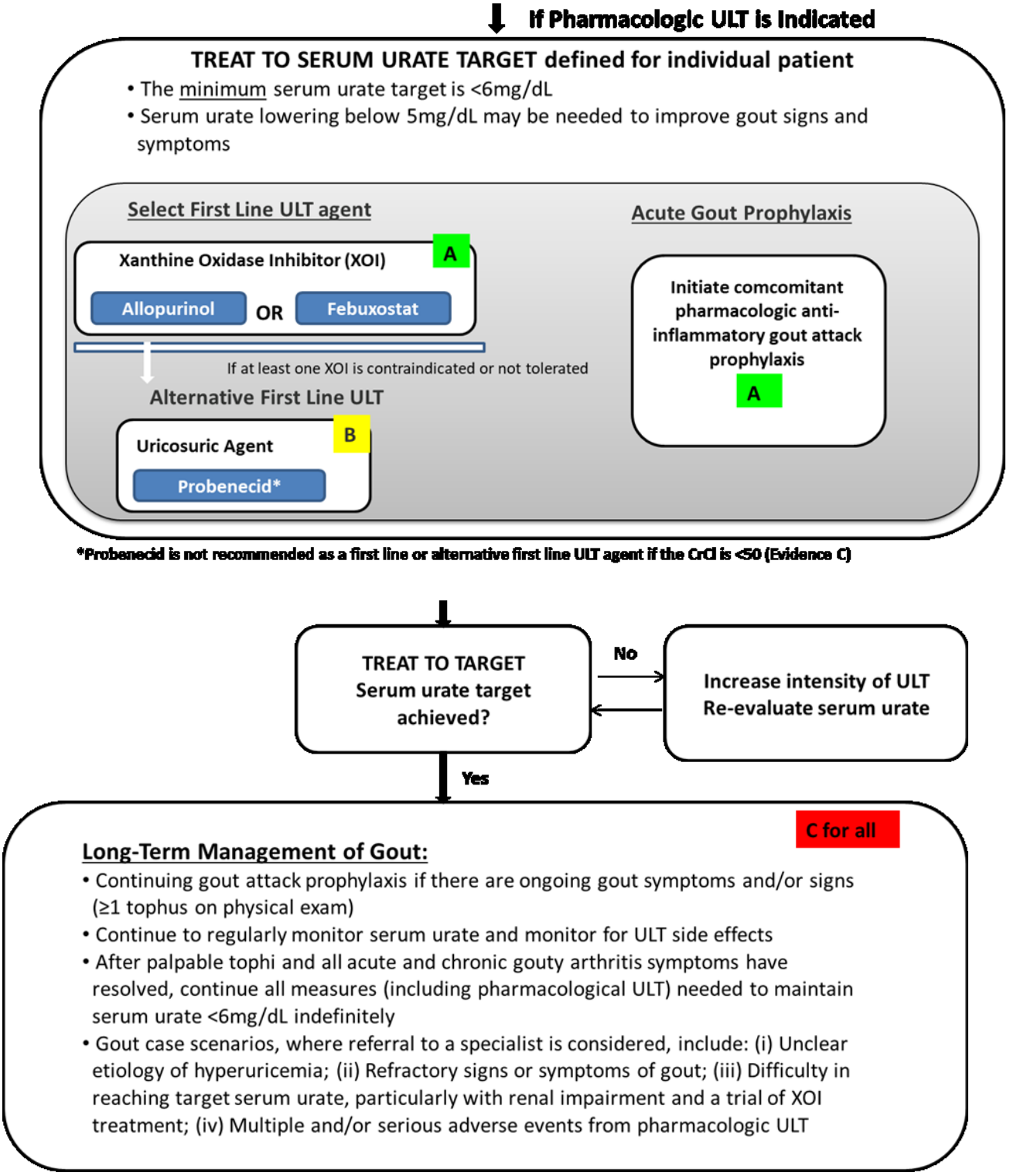
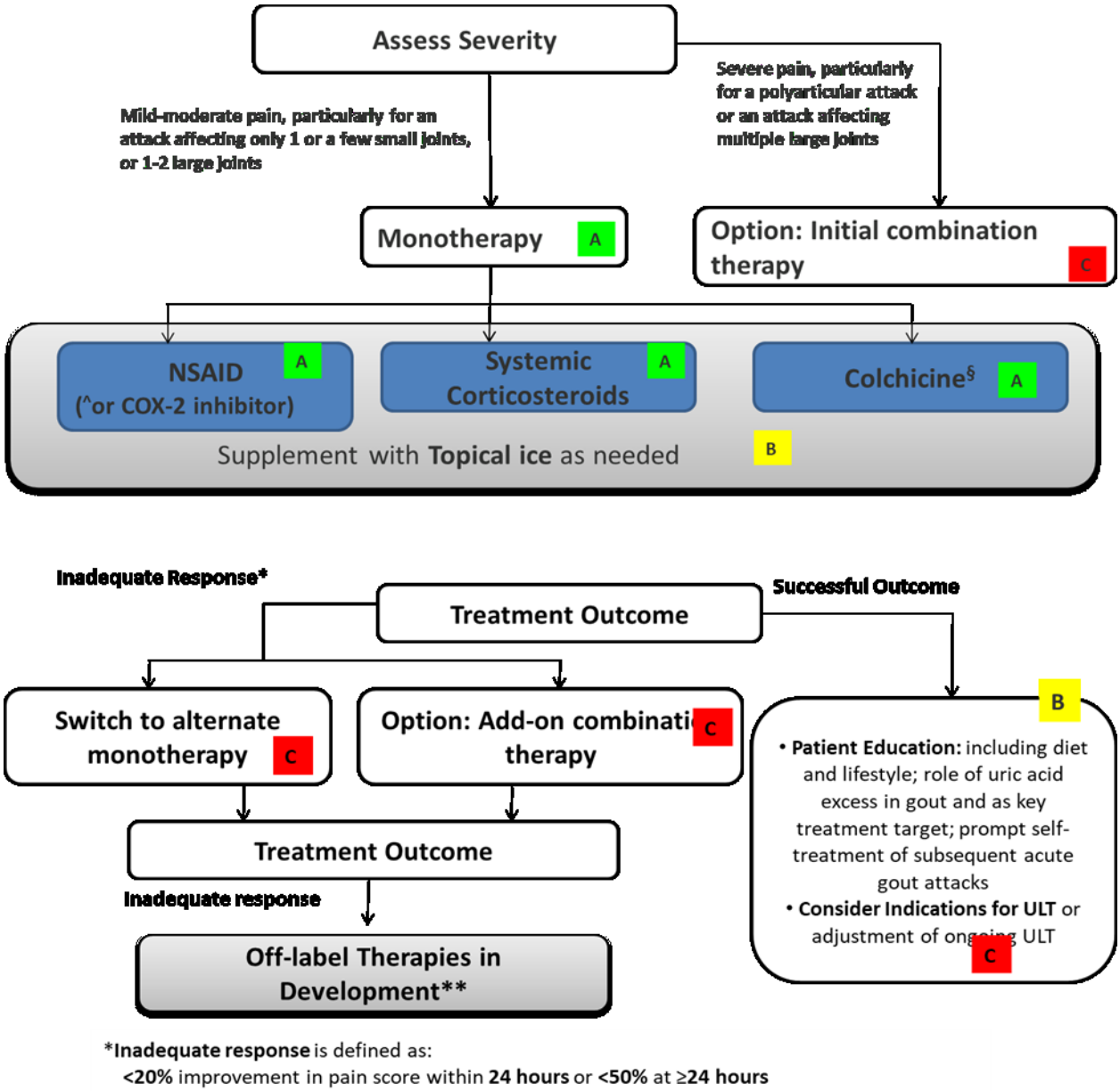

If Pharmacologic ULT is Indicated
TREAT TO SERUM URATE TARGET defined for individual patient
• The minimum serum urate target is <6mg/dL
• Serum urate lowering below 5mg/dL may be needed to improve gout signs and symptoms
Select First Line ULT agent
Xanthine Oxidase Inhibitor (XOI)
A
Allopurinol
OR
Febuxostat
If at least one XOI is contraindicated or not tolerated
Alternative First Line ULT
Uricosuric Agent
B
Probenecid*
Acute Gout Prophylaxis
Initiate comcomitant pharmacologic anti-inflammatory gout attack prophylaxis
A
*Probenecid is not recommended as a first line or alternative first line ULT agent if the CrCl is <50 (Evidence C)
TREAT TO TARGET
Serum urate target achieved?
No
Increase intensity of ULT
Re-evaluate serum urate
Yes
C for all
Long-Term Management of Gout:
• Continuing gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥1 tophus on physical exam)
• Continue to regularly monitor serum urate and monitor for ULT side effects
• After palpable tophi and all acute and chronic gouty arthritis symptoms have resolved, continue all measures (including pharmacological ULT) needed to maintain serum urate <6mg/dL indefinitely
• Gout case scenarios, where referral to a specialist is considered, include: (i) Unclear etiology of hyperuricemia; (ii) Refractory signs or symptoms of gout; (iii) Difficulty in reaching target serum urate, particularly with renal impairment and a trial of XOI treatment; (iv) Multiple and/or serious adverse events from pharmacologic ULT

Figure 5. ACR Gout Guidelines: Management of Acute Gout Attack [15]



Level A Grading	Supported by multiple (i.e. >1) randomized clinical trials or meta-analyses

Level B Grading	Derived from a single randomized trial or non-randomized studies
Level C Grading	Consensus opinion of experts, case studies, or standard-of-care

Management of Gout: Treatment Options "Allopurinol or Febuxostat"

The ACR guidelines recommend Febuxostat or Allopurinol as first line ULT. [14] Allopurinol remains the most commonly used medication for the treatment of gout. The recommended approach for determining the appropriate dose of allopurinol is to give a starting dose of 100 mg daily (and 50 mg/day in stage 4 or worse chronic kidney disease), with further 100-mg increments every 2 to 5 weeks until the target level of sUA is achieved. [14] In a retrospective study, it was reported that little more than 1/3 of treated patients reached the therapeutic goal of sUA <6 mg/dL while on Allopurinol. [16] Although Allopurinol is approved at doses of 100 to 800 mg daily, 95% of dosing in the US is at ≤300 mg daily [17] and many gout patients do not reach the goal serum urate range of 300 mg daily. [18] There are several factors contributing to low dosing of allopurinol, including intolerance (~10-15%), rare but life-threatening rashes, and hypersensitivity syndrome. [19] Dosage reduction is recommended with impaired renal function. [20]

Febuxostat is a novel nonpurine selective inhibitor of xanthine oxidase indicated for the chronic management of hyperuricemia in patients with gout. In randomized controlled trials, the efficacy of Febuxostat at 40 mg daily was reported comparable or superior to that of Allopurinol at 300 mg once daily, while 80 mg daily of Febuxostat was superior to Allopurinol at 300 mg.[18, 21, 22] In an open-label extension study it was reported that over 80% of the patients in the Febuxostat group and 46% of the patients in the Allopurinol group achieved the sUA <6.0 mg/dL

goal after 1 month of treatment,[23] with no significant difference between the treatment groups in the overall reported adverse event rates from any of the trials. [18] [21] [22] [23] Febuxostat was also more effective than Allopurinol in a subset of patients with impaired renal function, without the need for any dose adjustment in patients with mild-to-moderate renal impairment.[24]

The Purpose and Significance of this Study

The purpose of this project is to describe and examine factors associated with the long-term medication adherence of gout patients in a large sample of the U.S. population.

As mentioned above, adequate lowering of serum urate (sUA) to a target level of <6.0 mg/dl leads to the improvement of patients' QoL. Compliance of patients with chronic disease medications is one of the most important keys for gout management.

Poor compliance with gout medications has been recognized. Adherence to gout medications is remarkably low compared to the medication adherence of those with other chronic conditions. (More details about the previous studies will be discussed in the next chapter.) However, there is not enough research which represents the entire general population of patients in the U.S. with gout. Some of the previous studies had relatively large study populations and national coverage, but many of them lacked sufficient numbers and coverage to represent the whole U.S. population. As one of the reasons why relatively few studies about gout have been conducted, it is possible that people tend to underestimate the impact of gout on patients and society. Generally speaking, gout tends to be recognized as a "pain attack which can be treated with OTC medicines." But, as discussed above, the impact of gout on patients is not minimal from the

HRQOL perspectives and the burden on society. To improve the current situation, not only ad hoc responses but more root-cause treatment needs to be considered. It is hoped that the study of long-term medication adherence of gout patients will contribute to improving the current situation.

There has been no report to date from a gout medication adherence study in the U.S. that includes the relatively new treatment, Febuxostat. All of the previous studies reported the patient adherence for Allopurinol only because Febuxostat was launched in the U.S. market fairly recently (in 2009) and the market share is still not substantial. Even if the Febuxostat usage is not very prevalent, considering the potential effectiveness and benefits to patients, it may be meaningful to have a more comprehensive study of current gout medications. Therefore, this study of patient adherence, which includes both Allopurinol and Febuxostat with a large database covering the entire U.S., can make a meaningful contribution.

In this study, in addition to the adherence among the whole study population, the comparison between Allopurinol and Febuxostat in terms of adherence was also studied. As discussed above, Febuxostat is considered to be more effective than existing treatment options and high patients' satisfaction was reported. [25] At the same time, because Febuxostat is a brand medicine, the cost burden to patients is considered to be high. So far, there has been no report to compare the adherence between these two medications. Although this study has a data limitation regarding cost information because EMR data does not have the claims information, it can be considered meaningful to know the comparison of these two medications in order to consider better chronic gout management.

It is critical to understand the factors associated with chronic gout medication adherence to develop a plan to improve gout medication adherence. As I discuss in more detail in the literature review chapter, there are several key factors which have been considered related to medication adherence. For example, the type of prescribers (specialist vs non-specialist) had a significant impact on the adherence. This finding implies that physician and patient education may improve the outcome. If the related factors are adequately captured through this study, the information will be useful to develop the countermeasures to be taken. The positive impact will be brought to not only individual patients but also the society through the optimal utilization of medical resources and the improved productivity.

The Structure of this Dissertation

Following this chapter 1, I summarize the previous studies about adherence to chronic gout management as the results of the literature review in Chapter 2. From the previous studies' findings, I describe the relationships between outcomes and adherence, adherence in several populations, potential factors which have an impact on poor (good) adherence and other factors related to adherence in gout management.

In Chapter 3, I describe the methodology of this study, including the conceptual framework, data source, study population, study outcomes, covariates and analytic techniques.

In Chapter 4, I report all analysis results based on the methods which were described in Chapter 3. First, I describe the study population and its characteristics, then unadjusted/adjusted

adherence and sub-group analysis results (sub-groups by baseline flares or tophi and by baseline NSAIDS, steroids or colchicine).

In Chapter 5, I develop the discussion of findings from the analysis reported in Chapter 4 and present conclusions from this study. I also explore the implications for interventions to improve adherence based on this study's findings. In addition, I state the limitations of this study and suggestions for future study of these issues.

Chapter 2. Literature Review

Adherence and outcomes in chronic gout management

Several researchers have reported on the relationship between adherence and treatment outcomes in chronic gout management. Reach mentioned that poor adherence was the main factor limiting the effectiveness of gout treatment in a review of gout treatment in 2011. In this review, Reach also pointed out that poor adherence may be caused by the lack of prophylactic treatments and poor patient education about treatment-induced flares occurring at the beginning of ULT. [26]

Previous studies which reported adherence in chronic gout management

Several studies have been conducted to clarify the adherence to drug treatments for gout management and have pointed out the very low adherence rates. So far, all of the past research studies about chronic gout management in the U.S. have studied the adherence to Allopurinol only; no study has been conducted about the adherence to Febuxostat.

The following table summarizes the adherence data from previous studies about chronic gout management. A summary and discussion about each study follows.

Basically, all identified previous studies used the Medication Possession Ratio (MPR) to measure adherence. (Riedel. et al. used a different name in their report, but its calculation method is the same as the methods of MPR calculation. [27] The author was contacted and it was confirmed that it's identical with MPR.) An MPR of 80% (0.8) has been widely used as the threshold for good/poor adherence in previous research in many therapeutic areas and all

identified studies that reported adherence in chronic gout management also used this threshold. [28] [29]

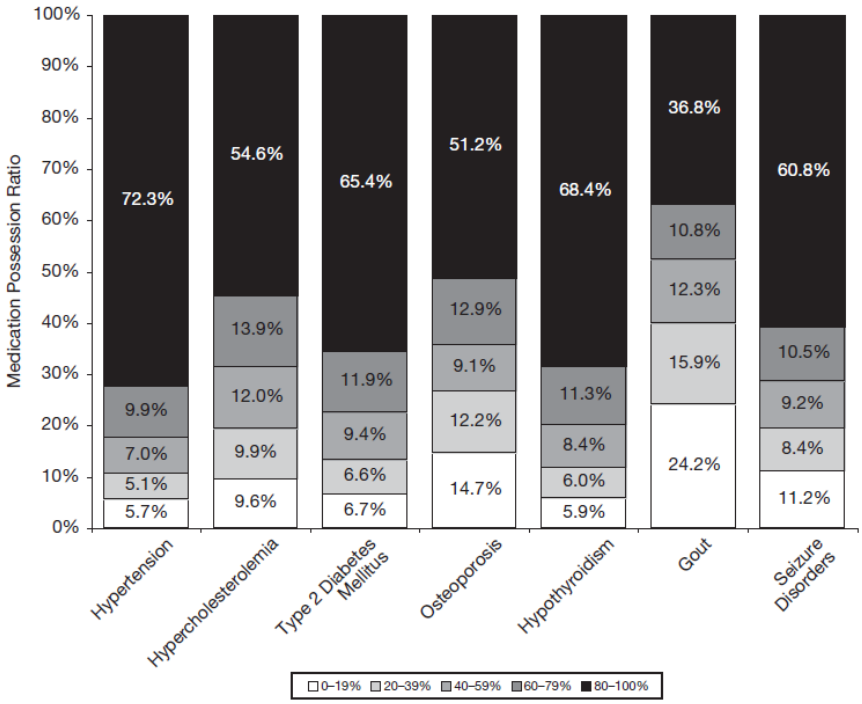
Table 2. Adherence data from past studies about chronic gout management

Author	Number of patients	Study population	MPR>80%	Note
Briesacher et al. (2008)[30]	9715	US population >18-year-old patients who had diagnosis of gout during study period 2001-2004	36.8%	Comparison of drug adherence among patients with 7 different conditions
Riedel et al. (2004) [27]	5597	US population Gout patients who filed at least 2 allopurinol prescriptions. Subjects identified from 1997-1998	18%	
Sarawate et al. (2006)[17]	2405	US population >18-year-old gout patients taking allopurinol. Data from 1999-2002	26%	
Harrold et al. (2008) [31]	4166	US population >18-year-old gout patients taking allopurinol. Data from 2000-2006	44%	

Solomon et al. (2008) [32]	9823	US population >65-year-old patients enrolled in pharmacy benefit program	36%	
Halpern et al. (2009) [33]	10,070	US population >18-year-old gout patients	44%	
Zandman-Goddard et al. (2013) [34]	7644	Israeli population >25 year--old patients with the diagnosis of gout treated with allopurinol identified over a 7-year period (2002-2009)	17%	

Briesacher et al. (2008) using MPRs, compared the chronic medication adherence among patients with gout, hypercholesterolemia, hypertension, hypothyroidism, osteoporosis, seizure disorders, and type 2 diabetes mellitus. The medication adherence among gout patients was the lowest level among all 7 different disease populations. [30]

Figure 6. Comparison of drug adherence rates across seven medical conditions. [30]



For patients with gout, MPRs increased with increasing comorbidities. Those with low comorbidity had a mean MPR of 52.3% (95% CI 51.4–53.3%), whereas those with high comorbidity had a mean MPR of 62.2% (95% CI 60.4–64.1%).

Riedel et al. (2004) examined compliance with allopurinol therapy among managed care enrollees with gout. They reported the lowest adherence rate (18%) among the several studies of gout medication adherence. In their study, the compliance with allopurinol was analyzed for 5597 subjects who filled at least 2 prescriptions for allopurinol. They reported that male gender was associated with decreased compliance, although the effect of gender diminished with increasing age. Increased compliance was associated with increasing age in both sexes and with the presence of diabetes or hypertension. [27] Their observation period (24 months) is relatively

long compared with other studies. It may be one explanation for their findings about the low adherence rate.

Sarawate et al. (2008) found low compliance with allopurinol as a medication for gout. They concluded that patients may receive suboptimal quality of care as measured by serum urate testing, and as measured by appropriate dosing of Allopurinol for those patients with renal impairment. In their study, 64.9% of allopurinol users had a modal daily dose or the most commonly observed daily dose of 300 mg/d, the median length of therapy was 3 months, and a high proportion of patients had a medication possession ratio of 10% or less. They found that 53% of patients with renal impairment received a modal daily dose of 300 mg or greater, and 83% of patients who started taking allopurinol did not have their serum urate levels measured within 180 days. They reported that patients with gout flares were less likely to be compliant with allopurinol (odds ratio, 0.50; 95% confidence interval,0.40-0.63) and patients with renal impairment at baseline were 3.2 times more likely to undergo serum urate testing than patients without renal impairment (odds ratio, 3.20; 95% confidence interval, 1.25-8.23). [17]

Harrold et al. (2009) reported 44% of their study population achieving an MPR > 0.80. The predictors of non-adherence included age less than 50 years, fewer comorbid conditions based on the Charlson score, no provider visits specifically for gout care prior to ULT initiation, and the use of NSAIDs in the year prior to ULT initiation. As other studies have suggested, they reported that younger and healthier patients with gout have a tendency toward lower adherence. They pointed out that this pattern may be related to lack of knowledge among patients with gout taking medicine. They reported that the lack of provider visits associated with a gout diagnosis

prior to ULT initiation was associated with non-adherence and pointed out the possibility that a face-to-face meeting focused on gout is needed to discuss the rationale and goals of medication treatment of gout. [31]

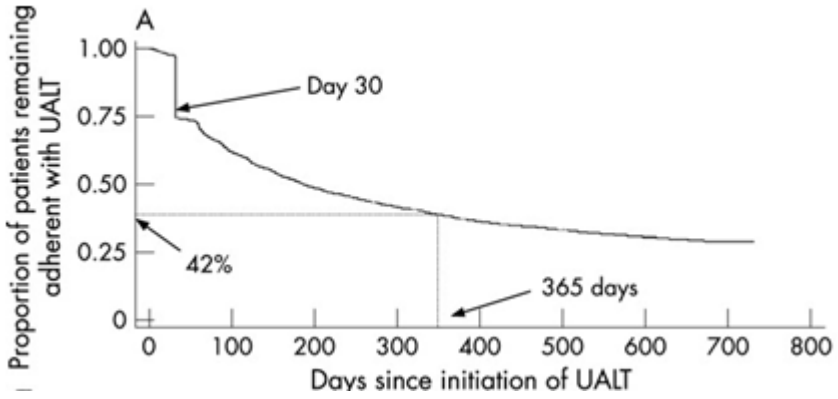
Solomon et al. (2008) assessed adherence with ULT over a 1-year study period among 9823 older patients (65 years old or older) and found poor adherence (36%) as other studies have reported. They reported that predictors of poor adherence included younger age (odds ratio (OR) 1.50, 95% CI 1.33–1.69 for ages 65–74 compared with 85 and above) and African–American race (OR 1.86, 95% CI 1.52–2.27 compared with Caucasian race). An interesting point of this study is that they found that treatment by non-specialists may be related to the poor adherence. Most patients (93%) received their initial ULT prescription from a non-specialist and this also predicted poor adherence (OR 1.15, 95% CI 0.96–1.38 compared with treatment by rheumatologists or nephrologists). [32]

Table 3. Adjusted logistic regression models for non-adherence; variables associated with less than 80% of days covered [32]

Patient variables	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
	All patients	Men only
Gender, male	1.00 (0.90–1.10)	NA
Age:		
65–74	1.50 (1.33–1.69)	1.64 (1.30–2.08)
75–84	1.35 (1.22–1.49)	1.28 (1.02–1.59)
85+	1.00	1.00
Race:		
African–American	1.86 (1.52–2.27)	1.87 (1.31–2.68)
Other	1.57 (0.96–2.58)	1.58 (0.51–4.94)
Caucasian	1.00	1.00
Health care utilisation:		
Acute care hospitalisations, none	1.18 (1.07–1.31)	1.04 (0.86–1.27)
Different drugs:		
0–7	1.40 (1.24–1.57)	1.59 (1.28–1.99)
8–12	1.19 (1.08–1.32)	1.06 (0.87–1.31)
13+	1.00	1.00
Comorbidity:		
0–1	1.35 (1.20–1.53)	1.36 (1.07–1.72)
2–3	1.12 (1.01–1.24)	1.30 (1.06–1.60)
4+	1.00	1.00
Gout related factors:		
Diagnosis of tophaceous gout, none	1.48 (1.03–2.12)	1.54 (0.72–3.29
Number of colchicine prescriptions, none	1.14 (1.00–1.29)	1.03 (0.81–1.31)
UALT prescriber, non-nephrologist, non-rheumatologist	1.15 (0.96–1.38)	1.09 (0.77–1.56)

They also developed a plot of the survival distribution of the time until an extended break occurred for all patients. It shows that about one-quarter of patients have an extended break in treatment after their first prescription and by 365 days, more than half have had an extended break in therapy. [32]

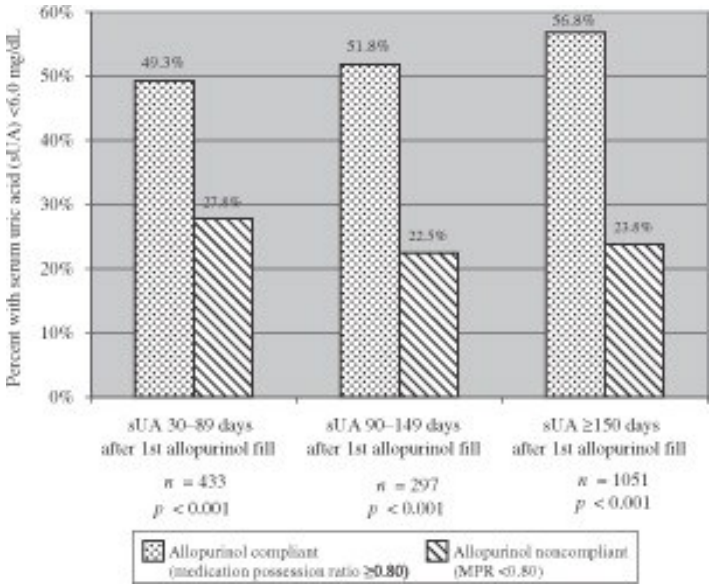
Figure 7. Plot of the proportion of patients who remained adherent (y-axis) with uric acid lowering therapy (UALT) as a function of duration since first prescription (x-axis).



Halpern et al. (2009) studied the relationships among Allopurinol compliance, sUA levels, and healthcare expenditures associated with gout. In their study, 44% of the 10070 patients with at least one Allopurinol prescription filled were compliant with an MPR >80%. [33]

They reported a strong association between medication compliance and sUA level. Unadjusted comparisons of allopurinol compliance by post-allopurinol sUA level showed a consistent association between compliance and sUA < 6.0 mg/dL. Among subjects with a sUA result 30–89 days after the first allopurinol fill, 49.3% of compliant users had sUA < 6.0 mg/dL compared with 27.8% of non-compliant users ($p < 0.001$). Among subjects with a sUA result in the 90–149 day period, 51.8% of compliant users had sUA < 6.0 mg/dL compared with 22.5% of non-compliant allopurinol users ($p < 0.001$). And among subjects with a sUA after 150 days, 56.8% versus 23.8% of compliant and non-compliant allopurinol users, respectively, had sUA < 6.0 mg/dL ($p < 0.001$). The findings support the importance of adherence improvement in gout management. [33]

Figure 8. Allopurinol compliance and serum uric acid <6.0 mg/dL [33]



Zandman-Goddard et al. (2013) studied 7644 patients in Israel and found only 17% of the study population were adherent to allopurinol therapy. Similar to previous studies, they found age and comorbidities are related to medication adherence. (Patients who were young upon initiation of allopurinol therapy were more prone to treatment discontinuation and people with other chronic disorders, in particular cardiovascular diseases, were found to be more compliant. They also pointed out that high flare rates may contribute to a loss of confidence in the benefit of the medication and may lead to subsequent poor adherence. [34]

Please see Appendix A for a detailed summary of the literature review.

Potential factors associated with adherence in chronic gout management

Lack of knowledge/patient education

As mentioned above, in a review of gout treatment Reach pointed out that poor adherence may be caused by poor patient education about treatment-induced flares occurring at the beginning of ULT. [26] At the onset of ULT, decreasing the sUA level by treatment may trigger the acute gout flares. It is known as the treatment-induced flare. According to Becker et al., the lowering of serum urate may cause the change in urate concentrations and trigger the flares. [35] Sometimes, patients misunderstand and believe that the further gout attack means the treatment is not working and stop taking the medicine, if they did not receive the adequate explanation before starting the ULT regarding possible flares just after the onset of treatment.

Harrold et al. also reported that the lack of provider visits associated with a gout diagnosis prior to ULT initiation was associated with non-adherence; they remarked that possibly a face-to-face meeting focused on gout is needed to discuss the rationale and goals of medication treatment of gout. [29]

Specialist vs Non-specialist

Beyond the challenge of patient education, the underlying root cause of lack of patient education might be a lack of knowledge and low adherence to the standard treatment guidelines among physicians.

Solomon et al. reported that a prescription from a non-specialist was one of the predictors of poor adherence to gout treatments. In their study, most patients (93%) received their initial ULT prescriptions from non-specialists and this predicted poor adherence (OR 1.15, 95% CI

0.96-1.38) compared with receiving prescriptions from specialists (rheumatologists or nephrologists).

Odera et al. pointed out that there is room to improve the physicians' treatment compliance with ACR guidelines among both primary care physicians (PCPs) and rheumatologists. Although both specialists and PCPs have room to improve, they reported that PCPs are less compliant with the treatment guidelines than rheumatologists. [36]

Patients' health status (with/without chronic disease)

Briesacher et al. reported that adherence was increased with the increase of comorbidity burden. They reported that this trend was found also for other chronic diseases (hypertension, hypercholesterolemia). [30] Riedel et al. reported that the increasing compliance was associated with the presence of diabetes or hypertension. [27] Zandman-Goddard, G., et al. also reported better compliance among those with comorbidities, particularly among patients with concomitant cardiovascular disease. [34]

Patients with other chronic diseases may have the custom to take medicines as part of their routines in everyday life. It may also be considered that patients with other comorbidities may tend to be concerned about their own health, which leads to the better adherence to gout treatments.

Patients' age and gender

Many researchers have reported that younger age was associated with the lower adherence. [30] [31] [32]

Riedel et al. reported that male gender was associated with decreased compliance, although the effect of gender diminished with increasing age and that increased compliance was associated with increasing age in both sexes. [27]

Other factors (marital status, socioeconomic status, BMI, race)

Zandman-Goddard et al. reported that non-married individuals, those of low socioeconomic status and those with lower BMI were associated with lower adherence. [34] Solomon et al. reported that African-American race was one of the predictors of poor adherence to gout treatments. (Solomon's study did not control for socioeconomic status.) [32]

The finding about the relationship between lower BMI and poor adherence is considered to be aligned with other findings that healthier patients are less adherent to gout treatments. Lower SES also may be a critical factor contributing to adherence to gout treatments. As I discussed above, gout sometimes is recognized as "just a pain that can be treated with cheap OTCs" among the general population. Considering this fact, those with lower SES may prefer to skip gout medications because of economic reasons.

Chapter 3. Methods

Conceptual Framework

To understand the mechanisms of medication adherence to gout management, the following conceptual framework was developed based on the conceptual framework used in a study of medication use among older adults (Age ≥50 years) by Murray et al. [37] and the findings from previous gout adherence studies.

Based on the conceptual framework by Murray et al. [37], there are 3 environment factors: 1) External Environment (e.g. Living conditions, Community environment, Weather), 2) Healthcare System (e.g. Availability of Medical Care, Policy, Insurance), and 3) Medication Use System (e.g. Reminder system.)

Regarding patient characteristics, there are also 3 factors: 1) Predisposing characteristics (e.g. sex, age, knowledge of disease, attitude to treatment), 2) enabling resources (e.g. insurance, money, transportation to pharmacy), and 3) Need factors (e.g. Number of flares, Tophi). Along with the conceptual framework used in the medication study by Murray et al. [37], the findings from previous gout studies which were discussed in Chapter 2 and are shown in Table 4 were also incorporated in the conceptual framework used in this study.

Table 4. Summary of findings from previous studies

Author	Covariates	Findings	Note
Briesacher et al. (2008)	age, sex, geographic residence, history of drug, type of health plan, and a comorbidity score calculated by using the Hierarchical Condition Categories risk adjuster	MPRs increased with increasing **comorbidities** and **ages**. History of drug use, health plan, the subject's geographic area of residence, or Sex did not influence adherence.	Comparison of drug adherence among patients with 7 different conditions. No Lab data
Riedel et al. (2004)	sex, age, prescription filled, comorbidity (diabetes, hypertension, Renal failure, Obesity, RA, Depression, OA)	**Sex** (female has better compliance), **Age**, **Diabetes** and **hypertension** are associated with increased compliance.	No Lab data
Sarawate et al. (2006)	age, sex, preindex comorbidities, newly or previously diagnosed gout, and gout flare before postindex serum urate testing	Patients with a **gout flare** before postindex serum urate testing were 50% less likely to be compliant. Patients with baseline **hypertension** were 44% more likely to be compliant.	No Lab data
Harrold et al. (2008)	age, sex, health care utilization (visits to providers for gout both prior to and after ULD initiation, all provider visits prior to ULD initiation, and number of hospitalizations prior to ULD initiation), specific comorbidities, medications.	Predictors of poor adherence included younger **age**, fewer **comorbid conditions**, no **provider visits** for gout prior to urate-lowering drug initiation, and **use of NSAID** prior to urate-lowering drug initiation	No Lab data
Solomon et al. (2008)	age, gender, race), medical care intensity (number of physician visits, number of different medications used, number of acute care hospitalisations), comorbid conditions, gout specific factors (the number of acute gout arthritis diagnoses; a diagnoses of nephrolithiasis; a diagnosis of tophi; a diagnosis of interstitial nephritis; the use of selective or non-selective NSAID, colchicine, or glucocorticoids and uric acid measurements), and physician characteristics (specialist or not)	Predictors of poor adherence included younger **age**, African–**American race** and prescription from **non-specialist physicians.**	No Lab data
Halpern et al. (2009)	sUA	Compliance was positively associated with **favorable sUA** in unadjusted comparisons.	Lab data (sUA only) - no other covariates
Zandman-Goddard et al. (2013)	age, sex, marital status, place of residency, years of stay in Israel, socio-economic level, chronic conditions, BMI, smoking	**Women aged** 45-64 years, **non-married** individuals, those of **low socioeconomic status** and those with **lower BMI** were more likely to discontinue therapy. Better compliance was achieved among those with **comorbidities.**	

The factors in green boxes in Figure 9 show those variables which are related to adherence in the previous studies. The factors in orange boxes in Figure 10 are those identified for the possible related factors in this study. After the analysis, future possible interventions are considered based on the findings.

Figure 9 Conceptual Framework of Gout Medication Adherence with the factors which are related to adherence in the previous studies.

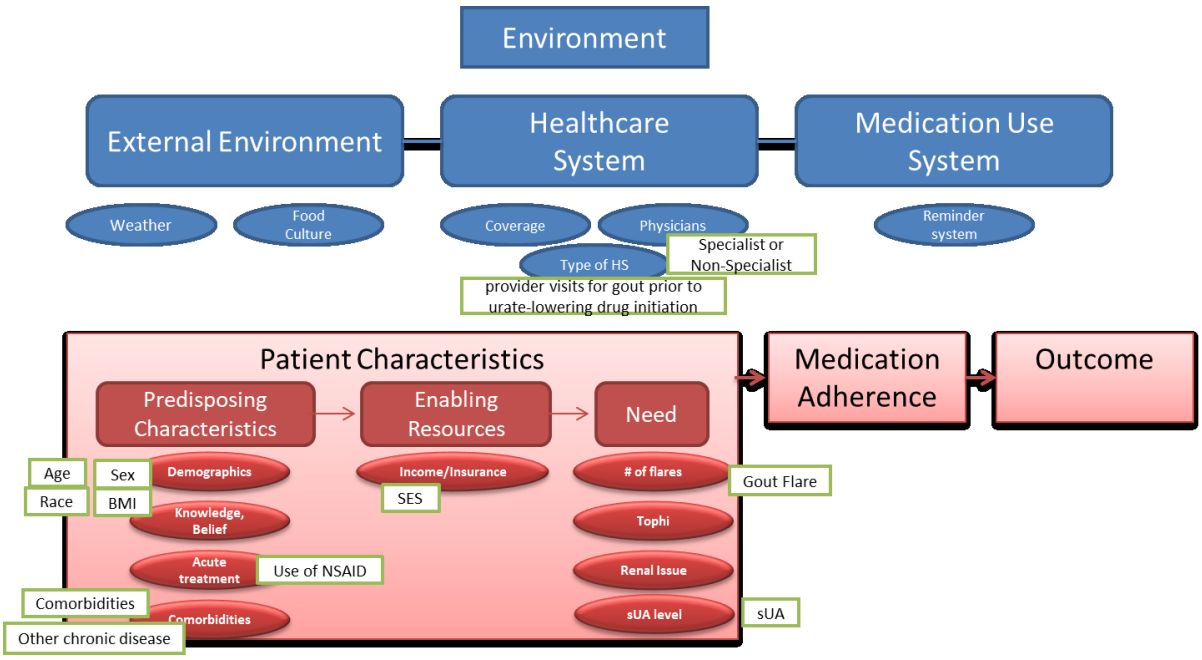
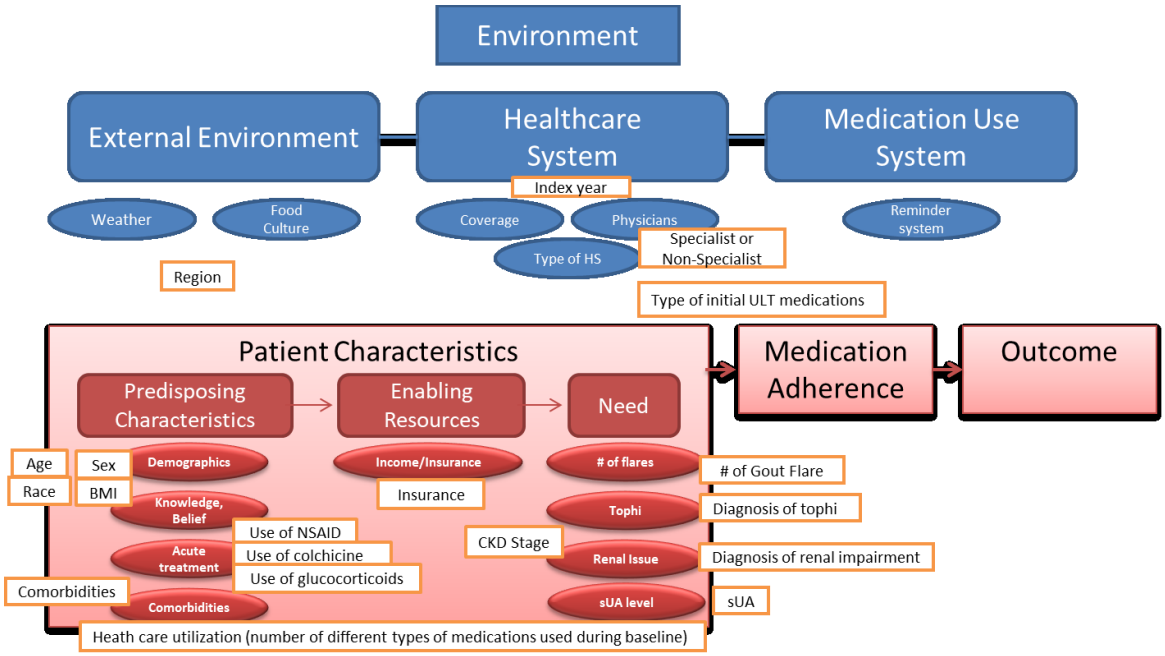


Figure 10 Conceptual Framework of Gout Medication Adherence with the factors which a which are studied in this study.



Data Source

This is a retrospective cohort study using the GE centricity electronic medical record (EMR) database. The data for the time period of January 1, 2009 through December 31, 2014 were used for this analysis. The GE centricity EMR database consists of longitudinal ambulatory electronic health data covering over 38 million U.S. patients in 49 states and Washington, D.C. The database contains patient information on demographics, laboratory test results, medication lists, prescriptions, and payment types. The GE Centricity EMR database captures patient-level clinical data elements obtained from the Centricity Physician Office EMR for Clinical Data Services (CDS) reporting.

The Centricity ambulatory care EMR and its predecessors have been used for over 20 years, are certified by the Certification Commission for Healthcare Information Technology (CCHIT), and were used by over 30,000 clinicians in the United States in 2009. Centricity CDS includes data provided by 7259 clinicians (including approximately 60% primary care providers and 40% specialists) at 98 installations with 133 unique provider members. CDS includes de-identified, standardized data on more than 8,900,000 patients; and the data on at least half of these patients spans more than 985 days, for a median of approximately 2.7 years of continuous care. [38]

One study assessed the external validity and generalizability of the GE Centricity EMR database and analytical results to the US population using the National Ambulatory Medical Care Survey (NAMCS) data, the distributions of demographics in the GE Centricity EMR database were found to be generally similar to that of the overall U.S. population as captured in the NAMCS data, although the GE Centricity EMR database shows higher proportions of visits by younger patients and by females.[38]

All study data were de-identified and compliant with the Health Insurance Portability and Accountability Act (passed by the U.S. Congress in 1996.) The JHSPH IRB reviewed the application for this study on May 6, 2015 and determined that the proposed activity described in the application would use de-identified existing data to examine medication adherence to Febuxostat/allopurinol among gout patients. Therefore, they concluded that this study did not qualify as human subjects research as defined by DHHS regulations 45 CFR 46.102 [39], and did not require IRB oversight (see Appendix B).

Statistics Software

The analyses for this study were generated using SAS software Ver 9.4. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Study Population

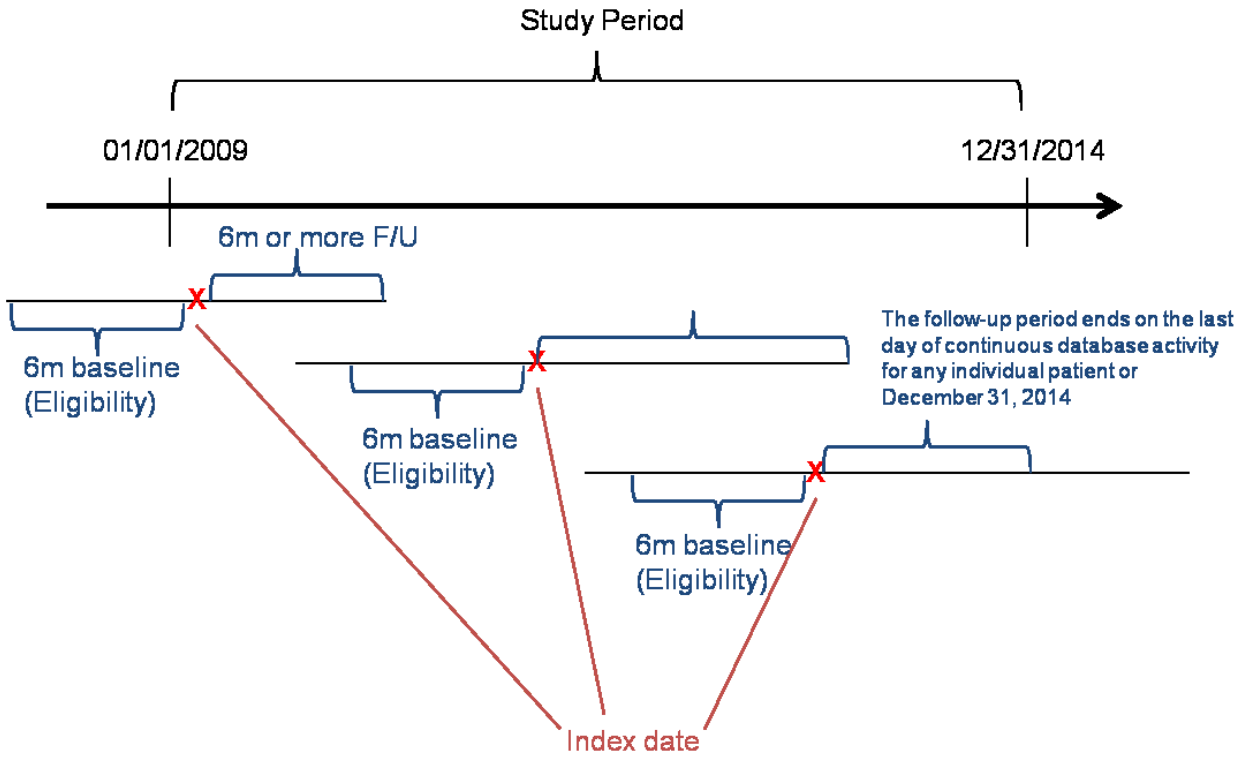
This study cohort included gout patients who received urate-lowering therapy (ULT) between January 1, 2009 and December 31, 2014. Subjects were included in the analysis if they met the following criteria: 1) Adult patients, ≥18 years of age at index date, 2) Diagnosed with gout (ICD-9, 274.xx) any time before (or on) the index date, 3) Newly treated with Allopurinol or Febuxostat on or after January 1, 2009, and 4) had continuous database activity for at least 6 months pre-index date (baseline period) and 6 months post-index date. The patients who used Allopurinol or Febuxostat at the baseline were excluded.

Table 5. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Adult patients, ≥18 years of age at index date 2. Diagnosed with gout (ICD-9, 274.xx) any time before (or on) the index date, 3. Newly treated with Allopurinol or Febuxostat on or after January 1, 2009, 4. Patients had continuous database activity (defined by flag of patient status in database) for at least 6 months pre-index date (baseline period) and 6 months post-index date.	1. The patients who used Allopurinol or Febuxostat at the 6 months pre-index date (baseline period) were excluded.

The follow-up period ends on the last day of continuous database activity for any individual patient or December 31, 2014. The last day of continuous database activity will mark the end of follow-up. Censoring for the persistence measure is described in Figure 11 below.

Figure 11. The study period: Censoring for the persistence measure



In this study, the switching between medications was not studied because of the data limitations.

Study Outcomes

Primary outcome: Adherence measured by Medication Possession Ratio (MPR)

In this study, adherence to ULT medication was measured by the Medication Possession Ratio (MPR), which is used widely to measure medication adherence for chronic disease(s). The following equation was used to compute MPR: The days' supply

of medication dispensed (excluding the last refill) divided by the number of days between the first and last prescription refill. [40]

$$MPR = \frac{\text{The days supply of medication dispensed in period}}{\text{Last prescription fill date} - \text{First fill date} + \text{Last fill days supply}}$$

As discussed in Chapter 2, an MPR of 80% (0.8) has been widely used as the threshold for good/poor adherence in a variety of studies covering many therapeutic areas. In addition, the previous studies that reported adherence in chronic gout management (Briesacher et al. (2008), Riedel et al. (2004), Sarawate et al. (2006), Harrold et al. (2008), Solomon et al. (2008), Halpern et al. (2009), Zandman-Goddard et al. (2013)) also used this threshold.

Secondary outcome: Persistence

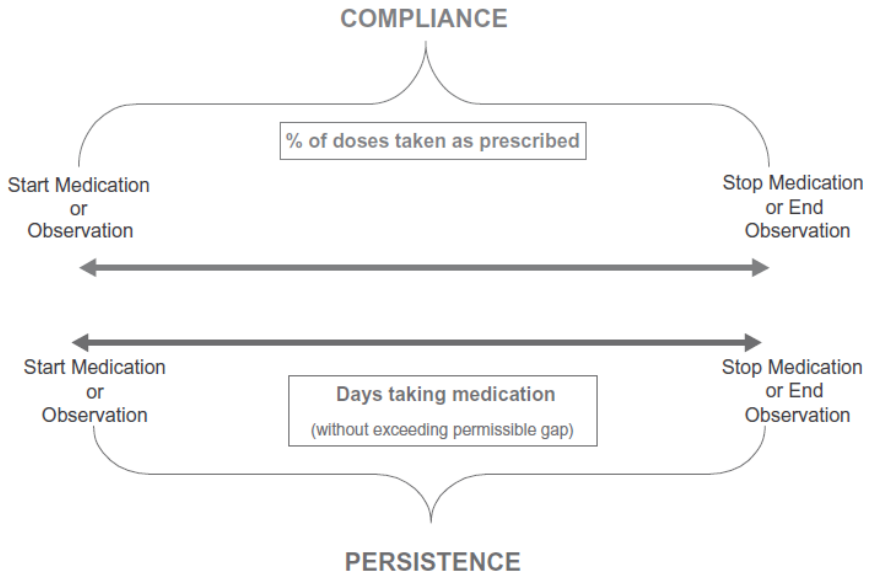
Persistence with ULTs was assessed as the time from the Index date until an extended break in treatment, defined as the first prescription gap of at least 60 days.

$$Persistence = Days\ (Years)\ taking\ medications\ without\ exceeding\ a\ 60\ days\ gap$$

Because MPR is calculated by the proportion of days during the follow-up period in which a patient has available medications, it is difficult to assess the patient's behavior. To understand more about patient behavior, persistence was analyzed in addition to adherence measured by the MPR. A similar analysis was conducted by Solomon et al. with their study population (more than 65 years old patients who enrolled in a pharmacy benefit program). This study follows the approach used by Solomon, et al. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Medication Compliance and Persistence Work Group (Cramer et al.) defined medication adherence (compliance) as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen" and medication persistence as "the duration of time from initiation to discontinuation of therapy." They pointed out that clinical outcomes of treatment are affected not only by how well patients take their medications but also by how long they take their medications and conclude that both sides should be considered to capture the comprehensive behavior. [41]

Figure 12. Definitions of compliance and persistence by Caramer et al. [41]



Leppe et al. also reported that the combination of an MPR and a persistency metric could provide timely information on the dynamics of patient medication adherence. [29]

Covariates (Potential Confounding Factors):

Covariates included the type of medication (Febuxostat or Allopurinol) of ULT, demographics (age, gender, race, region), insurance plan, Index year, body mass index (BMI), CKD stage defined by estimated glomerular filtration rate (eGFR), specialist (Rheumatologist / Nephrologist) vs. non-specialist provider classifications, a diagnosis of tophi, a diagnosis of renal impairment, serum uric acid measurements (sUA), number of diagnoses of acute gout arthritis (gout flares, separated from each other by at least 30 days), comorbidities (quantified with the Charlson Comorbidity Index (CCI)), the use of NSAIDs, colchicine, or glucocorticoids and uric acid measurements (sUA)), and heath care utilization (number of different types of medications used during baseline)

Table 6. List of Covariates

Covariates	Short Name	Value	Note
Febuxostat vs Allopurinol	FEBUX	1 (Febuxostat), 0 (Allopurinol)	
Age	AGE	18-44,45-64,65+	Adult patients (Age >18)
Gender	GEN	Male, Female, Missing	
Race	ETHN	Asian, Black, Hispanic, White, Other, Unknown	
Region	REG	Northeast, Midwest, South, West	
Insurance	INSU	Commercial, Medicare, Other, Unknown	
Index year	INDEX	2009, 2010, 2011, 2012, 2013, 2014	
BMI	BMI	Underweight, Normal weight, Pre-Obese, Obese	BMI values were used to classify patients as follows- underweight (BMI<18.5 kg/m2), normal weight (18.5-24.9 kg/m2), pre-obese (25.0-29.9 kg/m2), or obese (≥30 kg/m2).

Covariates	Short Name	Value	Note
CKD stage	CKDSTG	Stage 1 (eGFR ≥ 90), Stage 2 (GFR 60-89), Stage 3 (GFR 30-59), Stage 4 (eGFR < 30)	The following equation was used to compute eGFR: GFR (mL/min/1.73 m2) = 175 × (serum creatinine level)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American). [33]
Specialist vs. Non-specialist provider classifications	SPEC	1 (Specialist), 0 (Non-specialist)	Specialist: Rheumatologist and Nephrologist
Diagnosis of gout tophi	TOPHI	1 (Tophi), 0 (No tophi)	Tophi - 274.03 tophus, 274.81 ear, 274.82 non-ear, subset of gout (274.xx)
Diagnosis of renal impairment	RENAL	1 (Renal impairment), 0 (No renal impairment)	Renal impairment 580.xx–586.xx.
Serum uric acid measurements (sUA)	SUA	sUA < 6mg/dL, 6-6.99mg/dL, 7-7.99mg/dL, 8-8.99 mg/dL, ≥9 mg/dL	
Number of diagnoses of acute gout arthritis (gout flares, separated from each other by at least 30 days	FLARE	0, 1, 2-3	Gout flares 274.xx with NSAID, colchicine, glucocorticoids or joint aspiration/drainage within 7 days, OR 719.4x with colchicine within 7 days (≥ 30 days apart)
Comorbidities (Quantified with the Charlson Comorbidity Index (CCI))	CCI	0, 1, 2, 3	Comorbidities were quantified with the Charlson Comorbidity Index (CCI) using ICD-9 codes captured within the 6-month baseline period.
Use of NSAIDs	NSAID	1 (Use of NSAIDs), 0 (No Use of NSAIDs)	
Use of colchicines	Colchicine	1 (Use of colchicines), 0 (No Use of colchicines)	
Use of glucocorticoids	Steroid	1 (Use of glucocorticoids), 0 (No Use of glucocorticoids)	
heath care utilization (number of different types of medications used during baseline)	UTIL	0-1, 2-3, 4-6, 7-10, 11+	

Age groups included 18-44, 45-64 and 65 and over, based on the advice from Dr. Choi, an author of The American College of Rheumatology (ACR) Guidelines on the Management of Gout. Also, these are aligned with the age categories used in previous studies.

The Charlson Comorbidity Index (CCI) was used to quantify and consider the adjustment for comorbidities in this model. Although there exist newer models for the adjustment of comorbidities such as the Elixhauser approach, and there are discussions regarding which comorbidity model is the best approach for the database analysis [42], considering the comparability with the previous studies, I decided to use the CCI. All past studies which adjusted for comorbidities used the CCI.

Medications in the model list were as follows:

- Medication list
    - Febuxostat (Brand name Uloric): GPI_CATEGORY_4 = 'FEBUXOSTAT'
    - Allopurinol (Generic): GPI_CATEGORY_4 = 'ALLOPURINOL' or 'ALLOPURINOL SODIUM'
    - Colchicine (Colcrys): GPI_CATEGORY_4 = 'COLCHICINE'
    - NSAID: GPI_CATEGORY_2 = 'NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)'
    - Glucocorticoids (Generic): GPI_CATEGORY_1 = 'CORTICOSTEROIDS'

ICD-9 codes used in the model were as follows:

- Disease endpoint ICD-9 codes
    - Tophi - 274.03 tophus, 274.81 ear, 274.82 non-ear, subset of gout (274.xx)
    - Gout flares 274.xx with NSAID, colchicine, glucocorticoids or joint aspiration/drainage within 7 days, OR 719.4x with colchicine within 7 days (≥ 30 days apart)
    - Renal impairment 580.xx–586.xx.

Analytic Techniques

First, the baseline characteristics of the study population were examined for the whole study population and with a breakdown by medication.

Second, the MPR was used to estimate adherence and was examined for the whole study population and with a breakdown by medication. At first, the unadjusted MPR was calculated and examined by medication. Next, the MPR was used as the response in a logistic regression model with all covariates included in the model. When conducting a logistic regression model, it was defined that < 80% was considered poor adherence which is aligned with the definitions of previous studies. Initially, all covariates were considered potentially important and entered in the model. Variables adjusted for in the analytical model included all the covariates listed above. A stepwise

selection algorithm was used, and covariates with a p-value below 0.05 were retained in the model along with the indicator of Febuxostat. In the results all 19 covariates produced significant parameter estimates (p-values below 0.05.) The odds ratios and corresponding 95% confidence intervals for all significant covariates were reported.

$$logit(p) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_kX_k$$

$$odds = \frac{p}{1-p} = \frac{probability\ of\ presence\ of\ characteristic}{probability\ of\ absence\ of\ characteristic}$$

In addition, one-year adherence, truncating the follow-up at one year, was also calculated.

Then persistence of use was examined using Kaplan–Meier survival plots. Similar to the adherence analysis described above, at first, the unadjusted persistence was calculated and examined by medication. A Cox regression was fitted in the same manner as the MPR model above. A stepwise selection algorithm was applied to all the variables, and covariates with p-values below 0.05 were retained in the model along with the indicator of Febuxostat. As a result, 12 of the 19 available covariates were retained. More details of the stepwise process will be described in the results section. The hazard ratios and corresponding 95% confidence intervals for the significant covariates also will be reported.

Subgroup Analysis

In addition to the adherence and persistence analysis with the whole population, two subgroups were analyzed in terms of their unadjusted adherence and persistence, as well as their adjusted adherence: (i) patients who had tophi or at least one flare at baseline, and (ii) patients who were prescribed NSAIDs, steroids or colchicine at baseline. I conducted these sub analyses to examine: 1) the population with more severe gout (patients who had tophi or at least one flare at baseline are considered to be more severe gout patients) and 2) the patients with prophylaxis (NSAIDs, steroids or colchicine at baseline can be considered as prophylaxis to prevent gout flares).

The rationale is that the severity of disease status and prophylaxis might have major impacts on medication adherence based on the results from previous studies. Prophylaxis can prevent the treatment induced flares which are considered as a potential reason why patients stop taking medicine. These factors are included as covariates in the adjusted analysis, however it is considered to be meaningful to understand the patient behavior of the population who might have higher medical needs and those who might have more treatment induced flares.

Chapter 4. Results

Study Population

Figure 13 displays the whole study population. The total sample size for this study is 91,629 patients. The sample size of this study is much larger than those of previous studies which analyzed the medication adherence among patients with gout. (The largest sample size among previous studies was the one by Halpern et al. in 2009 with 10,070 patients.)

Figure 13. Patient Population

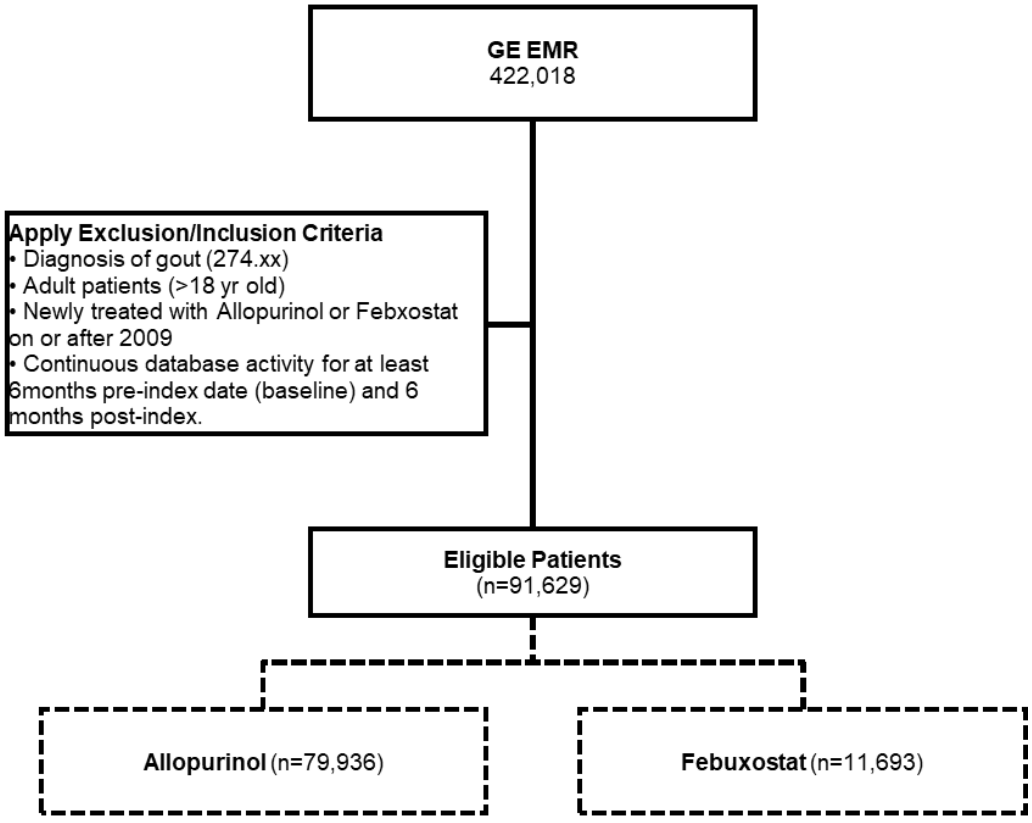


Table 7 displays the details of the patient selection process, which shows that the application of the inclusion and exclusion criteria reduced the initial population of 422,018 gout patients in the database to a final cohort of 91,629, consisting of 11,693 Febuxostat patients and 79,936 allopurinol patients.

Table 7 Study Population Selection Process

	Excluded	Remaining
Unique patients with gout in GEMS		422,018
Prescribed Allopurinol or Febuxostat prior to Index date	180,236	
		241,782
Index date in [2009, 2014]	50,863	
		190,919
Age≥18 and gout Diagnosis prior to Index date	31,446	
		159,473
At least 6 months of baseline and follow-up	64,376	
		95,097
Baseline free of index ULT	3,468	
		91,629
Final Cohort		**91,629**
*Group by medications Allopurinol patients Febuxostat patients		 79,936 11,693

Population Characteristics

Table 8 displays the baseline characteristics of the population. Patients are mostly male (73.0%), White (66.9%), and over-weight (pre-obese (23.6%) and obese (52.3%)). The average age is 63.3 years old and more than 90% of patients are over 45 years old

and more than 50% of patients are over 65 years old. Patient population characteristics are similar to those of previous studies.

Having the laboratory data is one of the strengths of this database. However, there are many missing values in the laboratory data: 52.0% of patients in the study don't have sUA data and 37.2% of patients don't have CKD stage information. It is one of the limitations of this retrospective database study. The distributions of those with missing data for sUA and CKD are not so different from the whole study population. Clinicians and previous studies have pointed out that many non-specialist (e.g. GP/Family medicine doctors) don't comply with the guidelines and they don't order the sUA check although it is suggested in the guideline. [36] Therefore, missing data for sUA might not be random, but rather imply the low compliance of physicians to the guidelines. However, it is difficult to identify the real reason in this study because of the data limitations.

Table 8. Study Population Characteristics (entire study population) (N, %)

		N (%)
Gender	Male	66846 (73.0%)
Age	mean years	63.3 (SD: 13)
Age Group	18-44 years	9027 (9.9%)
	45-64	35881 (39.2%)
	65+	46721 (51.0%)
Ethnicity	Asian	1739 (1.9%)
	Black	9506 (10.4%)
	Hispanic	1024 (1.1%)
	White	61267 (66.9%)
	Other	2205 (2.4%)
	Unknown	15888 (17.3%)

Region	Northeast	23300 (25.4%)
	Midwest	15828 (17.3%)
	South	33565 (36.6%)
	West	18936 (20.7%)
Insurance	Commercial	18457 (20.1%)
	Medicare	38682 (42.2%)
	Other	2697 (2.9%)
	Unknown	31793 (34.7%)
Index year	2009	17362 (18.9%)
	2010	16710 (18.2%)
	2011	20067 (21.9%)
	2012	19875 (21.7%)
	2013-14	17615 (19.2%)
BMI	Underweight	247 (0.3%)
	Normal	6956 (7.6%)
	pre-Obese	21623 (23.6%)
	Obese	47889 (52.3%)
	Missing	14914 (16.3%)
CKD Stage	Stage1, eGFR >= 90	6152 (6.7%)
	Stage 2, eGFR 60-89	22866 (25.0%)
	Stage 3, eGFR 30-59	23996 (26.2%)
	Stage4+, eGFR < 30	4543 (5.0%)
	Missing	34072 (37.2%)
Uric Acid	sUA < 6	5527 (6.0%)
	sUA 6-6.99	4668 (5.1%)
	sUA 7-7.99	8062 (8.8%)
	sUA 8-8.99	9980 (10.9%)
	sUA ≥ 9	15787 (17.2%)
	Missing	47605 (52.0%)

Type of physician: Specialist or not	Specialist (Rheumatologist and Nephrologist)	5387 (5.9%)
Tophi or not	Tophi	800 (0.9%)
Renal impairment or not	Renal impairment	7208 (7.9%)
Flares	0	79713 (87.0%)
	1	11755 (12.8%)
	2-3	161 (0.2%)
Charlson Comorbidity Index	0	74031 (80.8%)
	1	7689 (8.4%)
	2	7009 (7.6%)
	3+	2900 (3.2%)
NSAIDs Use or not	NSAIDs	26389 (28.8%)
Steroids Use or not	Steroids	17506 (19.1%)
Colchicine Use or not	Colchicine	17911 (19.5%)
Utilization	0-1 Med	20365 (22.2%)
	2-3 Meds	16283 (17.8%)
	4-6 Meds	23034 (25.1%)
	7-10 Meds	19214 (21.0%)
	11+ Meds	12733 (13.9%)

Table 9 displays the baseline characteristics of the population by type of ULT. While the Febuxostat and Allopurinol cohorts are similar in age, sex, ethnic background and insurance distributions, there are some differences by region, index year and other variables. While some of the differences appear to be minimal—for example in gender—the p-values for the differences between the two cohorts, driven by the large sample sizes, are very small.

Overall, the Febuxostat treatment group has more patients from the South and less from the Northeast, more people who start treatment in the latter Index years, more obese patients, higher numbers in the latter stages of CKD, fewer patients with missing uric acid test results, and more who received their first prescription from a specialist. Additionally, the Febuxostat cohort has a larger percentage of patients with renal impairment, taking steroids, colchicine and different types of medications (health utilization), painting a picture of a somewhat sicker population compared to the Allopurinol group.

Table 9. Population Characteristics (n, % or quantity) by treatment groups

		TOTAL N=91,629	**Allopurinol N=79,936**	**Febuxostat N=11,693**	**p-value**
Gender	Male	66846 (73.0%)	58442 (73.1%)	8404 (71.9%)	0.005
Age	mean years	63.3 (SD 13)	63.4 (SD 13)	62.7 (SD 13)	<0.0001
Age Group	18-44 years	9027 (9.9%)	7709 (9.6%)	1318 (11.3%)	<0.0001
	45-64	35881 (39.2%)	31321 (39.2%)	4560 (39.0%)	
	65+	46721 (51.0%)	40906 (51.2%)	5815 (49.7%)	
Ethnicity	Asian	1739 (1.9%)	1471 (1.8%)	268 (2.3%)	<0.0001
	Black	9506 (10.4%)	8138 (10.2%)	1368 (11.7%)	
	Hispanic	1024 (1.1%)	899 (1.1%)	125 (1.1%)	
	White	61267 (66.9%)	53397 (66.8%)	7870 (67.3%)	
	Other	2205 (2.4%)	1933 (2.4%)	272 (2.3%)	
	Unknown	15888 (17.3%)	14098 (17.6%)	1790 (15.3%)	
Region	Northeast	23300 (25.4%)	20876 (26.1%)	2424 (20.7%)	<0.0001
	Midwest	15828 (17.3%)	14076 (17.6%)	1752 (15.0%)	
	South	33565 (36.6%)	28194 (35.3%)	5371 (45.9%)	

	West	18936 (20.7%)	16790 (21.0%)	2146 (18.4%)	
Insurance	Commercial	18457 (20.1%)	16143 (20.2%)	2314 (19.8%)	<0.0001
	Medicare	38682 (42.2%)	33646 (42.1%)	5036 (43.1%)	
	Other	2697 (2.9%)	2446 (3.1%)	251 (2.1%)	
	Unknown	31793 (34.7%)	27701 (34.7%)	4092 (35.0%)	
Index year	2009	17362 (18.9%)	16251 (20.3%)	1111 (9.5%)	<0.0001
	2010	16710 (18.2%)	14487 (18.1%)	2223 (19.0%)	
	2011	20067 (21.9%)	17084 (21.4%)	2983 (25.5%)	
	2012	19875 (21.7%)	17068 (21.4%)	2807 (24.0%)	
	2013-14	17615 (19.2%)	15046 (18.8%)	2569 (22.0%)	
BMI	Underweight	247 (0.3%)	213 (0.3%)	34 (0.3%)	<0.0001
	Normal	6956 (7.6%)	6001 (7.5%)	955 (8.2%)	
	pre-Obese	21623 (23.6%)	18889 (23.6%)	2734 (23.4%)	
	Obese	47889 (52.3%)	41236 (51.6%)	6653 (56.9%)	
	Missing	14914 (16.3%)	13597 (17.0%)	1317 (11.3%)	
CKD Stage	Stage 1	6152 (6.7%)	5525 (6.9%)	627 (5.4%)	<0.0001
	Stage 2	22866 (25.0%)	20266 (25.4%)	2600 (22.2%)	
	Stage 3	23996 (26.2%)	20132 (25.2%)	3864 (33.0%)	
	Stage 4+	4543 (5.0%)	3478 (4.4%)	1065 (9.1%)	
	Missing	34072 (37.2%)	30535 (38.2%)	3537 (30.2%)	
Uric Acid	sUA < 6	5527 (6.0%)	4472 (5.6%)	1055 (9.0%)	<0.0001
	sUA 6-6.99	4668 (5.1%)	3893 (4.9%)	775 (6.6%)	
	sUA 7-7.99	8062 (8.8%)	6962 (8.7%)	1100 (9.4%)	
	sUA 8-8.99	9980 (10.9%)	8618 (10.8%)	1362 (11.6%)	
	sUA ≥ 9	15787 (17.2%)	13085 (16.4%)	2702 (23.1%)	
	Missing	47605 (52.0%)	42906 (53.7%)	4699 (40.2%)	
Type of physician: Specialist or not	Specialist	5387 (5.9%)	4053 (5.1%)	1334 (11.4%)	<0.0001
Tophi or not	Tophi	800 (0.9%)	605 (0.8%)	195 (1.7%)	<0.0001

Renal impairment or not	Renal impairment	7208 (7.9%)	5916 (7.4%)	1292 (11.0%)	<0.0001
Flares	0	79713 (87.0%)	69772 (87.3%)	9941 (85.0%)	<0.0001
	1	11755 (12.8%)	10037 (12.6%)	1718 (14.7%)	
	2-3	161 (0.2%)	127 (0.2%)	34 (0.3%)	
Charlson	0	74031 (80.8%)	64771 (81.0%)	9260 (79.2%)	<0.0001
	1	7689 (8.4%)	6753 (8.4%)	936 (8.0%)	
	2	7009 (7.6%)	5924 (7.4%)	1085 (9.3%)	
	3+	2900 (3.2%)	2488 (3.1%)	412 (3.5%)	
NSAIDs Use or not	NSAIDs	26389 (28.8%)	22600 (28.3%)	3789 (32.4%)	<0.0001
Steroids Use or not	Steroids	17506 (19.1%)	13990 (17.5%)	3516 (30.1%)	<0.0001
Colchicine Use or not	Colchicine	17911 (19.5%)	14304 (17.9%)	3607 (30.8%)	<0.0001
Utilization	0-1 Med	20365 (22.2%)	19028 (23.8%)	1337 (11.4%)	<0.0001
	2-3 Meds	16283 (17.8%)	14508 (18.1%)	1775 (15.2%)	
	4-6 Meds	23034 (25.1%)	19865 (24.9%)	3169 (27.1%)	
	7-10 Meds	19214 (21.0%)	16254 (20.3%)	2960 (25.3%)	
	11+ Meds	12733 (13.9%)	10281 (12.9%)	2452 (21.0%)	

Unadjusted Adherence

The basic statistics for the unadjusted adherence are displayed in Table 10. In the whole study sample, patients were prescribed an average of 374 days' supply of drug (median: 210 days) over a mean follow-up period of 2.2 years. Following established convention in the literature, which regards an adherence of at least 80% as "adequate," this study found that

32.0% of patients achieved a personal adherence of at least 80%. The overall mean adherence was 46.4%. These numbers are aligned with those which were reported by previous studies. (Table 2, Appendix B)

The same basic statistics are displayed at the bottom of Table 10 for the case when the follow-up is limited to the first year after the Index date. During their first year on medication, patients were prescribed an average of 181 days' supply of drug (median: 150 days) over an average follow-up period of 0.83 years; 51.0% of patients achieved a personal adherence of at least 80%. The overall average adherence was 59.5%.

Table 10. Unadjusted Adherence Analysis Results (Full period, 1 year)

Supply: mean, median (SD) days	374, 210 (428)
Follow-up: mean (SD) years	2.2 (1.4)
Individual Adherence ≥ 80%	29,315 (32.0%)
Average Adherence	**46.4 %**
Supply 1-year: mean, median (SD) days	181, 150 (147)
Follow-up: mean (SD) years	0.83 (0.3)
Individual Adherence ≥ 80%	46,725 (51.0%)
Average Adherence	**59.5 %**

Table 11 shows the basic statistics of unadjusted adherence by medication groups. Allopurinol patients were prescribed an average of 396 days' supply of drug over an average follow-up period of 2.3 years, while Febuxostat patients were prescribed an average of 227

days' supply of drug over an average follow-up period of 1.6 years. 32.2% of Allopurinol patients achieved a personal adherence of at least 80%, compared to 30.4% of the Febuxostat group. The overall average adherence for the Allopurinol cohort was 47.1%, which was substantially higher than the Febuxostat average of 39.0%. Due to the large sample sizes, confidence intervals around these averages were very tight.

Similar to the statistics reported in Table 10, the same basic statistics appear at the bottom of Table 11 for the case when the follow-up is limited to the first year after the index date. During their first year on medication, Allopurinol patients were prescribed an average of 188 days' supply of drug over an average follow-up period of 10 months, while Febuxostat patients were prescribed an average of 134 days' supply of drug over an average follow-up period of 9 months. Further, 52.1% of allopurinol patients achieved a personal adherence of at least 80%, compared to 43.2% of the Febuxostat group. The overall average adherence for the Allopurinol cohort during the first year was 60.6%, compared to the Febuxostat average of 50.5%.

Table 11. Unadjusted Adherence Analysis Results by medications (Full period, 1 year)

	Total N=91,629	**Allopurinol N=79,936**	**Febuxostat N=11,693**
Supply: mean, median (SD) days	374, 210 (428)	396, 240 (439)	227, 90 (306)
Follow-up: mean (SD) years	2.2 (1.4)	2.3 (1.4)	1.6 (1.3)
Individual Adherence ≥ 80%	29,315 (32.0%)	25,758 (32.2%)	3,557 (30.4%)
Average Adherence	**46.4 %**	**47.1 %**	**39.0%**
Supply 1-year: mean, median (SD) days	181, 150 (147)	188, 180 (148)	134, 60 (133)
Follow-up: mean (SD) years	0.83 (0.3)	0.85 (0.3)	0.73 (0.4)
Individual Adherence ≥ 80%	46,725 (51.0%)	41,676 (52.1%)	5,049 (43.2%)
Average Adherence	**59.5 %**	**60.6 %**	**50.5%**

It must be pointed out that the quality of the Centricity EMR data left much to be desired. The days' supply was missing in about 44% of all the records. In those cases, a supply of 30 days was imputed, as 30 days was reported in 40% of the non-missing prescription lengths, by far the most frequent day count. Also, 30 days (1 month) is considered to be a reasonable assumption as the usual days of supply based on advice from Dr. Choi, an expert in gout and an author of the ACR Gout Guidelines.

Adjusted Adherence

A logistic regression was used to model adherence. All 19 covariates produced statistically significant parameter estimates, i.e. p-values below 0.05. Using the "Days on drug/Total days" as the "k/n" ratio for the dependent variable led SAS to interpret each day on drug as an "event" and each of the total days as a "trial," effectively leading to very large sample sizes. This approach, which allowed a natural estimate of adherence for each cohort in the unadjusted model, resulted in all covariates being significant with inordinately tight confidence intervals.

Table 12 displays the estimated odds ratios together with their 95% confidence intervals. The odds ratio for treatment was 0.654, meaning that after controlling for the covariates in this model, the Febuxostat adherence was significantly lower than that of Allopurinol. Applying equation (3.40) of Lachin (2000) [43] to the average adherence for the Allopurinol cohort of 47.1%, yields 36.8% as the average adherence for Febuxostat, a slightly lower adherence than the unadjusted estimate. Among the ethnic groups, only Asians (OR: 1.267) had a higher adherence than Caucasians statistically. Black (OR: 0.970) and Hispanic (0.899) patients had a lower adherence than Caucasians statistically. Looking by region, people in the Northeast had the highest adherence (OR: 1.155 to Midwest (reference)), while those in the South had the lowest (OR: 0.754 to Midwest (reference)), although these regional differences may also at least partly reflect differences in the quality of data. People on commercial health insurance plans had the highest adherence, compared to those on Medicare and others although there are possible confounders including age. Those who started on an ULT in 2009 had a relatively high adherence, topped only by the most recent

users, people with index years 2013-14. Compared to patients with stage 1 (or no) CKD, those with stage 4+ CKD (OR: 0.849) had worse adherence, but those with stages 2 (OR: 1.108) or 3 (OR: 1.059) had higher adherence. Uric acid levels appear to be a good predictor of adherence, as higher uric acid levels tend to be associated with better adherence. Patients with sUA6-6.99 (OR: 1.044), sUA7-7.99 (OR: 1.067), sUA 8-8.99 (1.145) and those with sUA>9 (OR: 1.200) had higher adherence than those with sUA<6. Patients treated by specialists (Rheumatologist/Nephrologist) had higher adherence (OR: 1.118) than those treated by non-specialists. Patients with tophi had higher adherence (OR: 1.136) than those without tophi. Patients using NSAID/Steroid/Colchicine (these medicines can prevent the ULT induced flare) had higher adherence than those not using these medications. This finding might imply that ULT induced flares are related to low adherence.

The more medications the patients were on, the higher adherence to gout treatment. Patients with 2-3 medications (OR: 1.261), those with 4-6 medications (OR: 1.348), those with 7-10 medications (OR: 1.479) and those with 11+ medications (OR:1.528) had higher adherence than those with 0-1 medications. While the overall Comorbidity index (Charlson scores) were low (less comorbidity), adherence seemed to decrease as the score increased. This finding implies that patients with more comorbidities had lower adherence.

Table 12. Odds Ratio Estimates of Adjusted Adherence Analysis

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
Febuxostat (1) vs Allopurinol (0)	0.654	0.653	0.656
Gender: Male (1) vs Female (0)	1.029	1.028	1.030

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
Age: 45-64 vs 18-44	1.136	1.134	1.138
Age: 65+ vs 18-44	1.105	1.103	1.107
Race: Asian vs White	1.267	1.262	1.271
Race: Black vs White	0.970	0.968	0.972
Race: Hispanic vs White	0.899	0.895	0.903
Race: Other vs White	0.826	0.823	0.829
Race: Unknown vs White	0.816	0.815	0.817
Region: Northeast vs Midwest	1.155	1.153	1.157
Region: South vs Midwest	0.754	0.753	0.755
Region: West vs Midwest	0.808	0.807	0.810
Insurance: Medicare vs Commercial	0.832	0.831	0.834
Insurance: Other vs Commercial	0.519	0.517	0.520
Insurance: Unknown vs Commercial	0.889	0.888	0.890
Index Year: 2010 vs 2009	0.815	0.813	0.816
Index Year: 2011 vs 2009	0.874	0.872	0.875
Index Year: 2012 vs 2009	0.928	0.926	0.930
Index Year: 2013-14 vs 2009	1.157	1.154	1.160
BMI: Missing vs Normal	0.956	0.954	0.958
BMI: Obese vs Normal	1.112	1.110	1.114
BMI: Underweight vs Normal	0.999	0.989	1.009
BMI: pre-Obese vs Normal	1.050	1.048	1.052
CKD stage: Stage 4+ vs Stage 1	0.849	0.847	0.852

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
CKD stage: Stage 3 vs Stage 1	1.059	1.056	1.061
CKD stage: Stage2 vs Stage 1	1.108	1.105	1.110
CKD stage: Missing vs Stage 1	0.931	0.929	0.933
SUA: sUA 6-6.99 vs sUA < 6	1.044	1.041	1.047
SUA: sUA 7-7.99 vs sUA < 6	1.067	1.064	1.070
SUA: sUA 8-8.99 vs sUA < 6	1.145	1.142	1.148
SUA: sUA ≥ 9 vs sUA < 6	1.200	1.198	1.203
SUA: Missing vs sUA < 6	0.821	0.819	0.823
Specialist (1) vs Non-specialist (0)	1.088	1.086	1.091
Tophi (1) vs Non-Tophi (0)	1.136	1.130	1.143
Renal impairment (1) vs Non-Renal impairment (0)	1.056	1.053	1.060
Number of Flares 1 vs 0	1.005	1.003	1.006
Number of Flares 2-3 vs 0	0.959	0.948	0.971
Charlson Index 1 vs 0	0.878	0.877	0.880
Charlson Index 2 vs 0	0.830	0.828	0.833
Charlson Index 3+ vs 0	0.723	0.720	0.725
NSAID use (1) vs No NSAID use (0)	1.053	1.052	1.054
Steroid Use (1) vs No Steroid Use (0)	1.056	1.054	1.057
Colchicine Use (1) vs No Colchicine Use (0)	1.092	1.090	1.093
Utilization: 2-3 Meds vs 0-1 Med	1.261	1.259	1.263
Utilization: 4-6 Meds vs 0-1 Med	1.348	1.346	1.350
Utilization: 7-10 Meds vs 0-1 Med	1.479	1.476	1.481

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
Utilization: 11+ Meds vs 0-1 Med	1.528	1.525	1.530

One-year Adherence

Truncating the follow-up at one year yielded almost identical results to the full period. Again, all the covariates produced significant parameter estimates, with the magnitudes of the odds ratios being very similar. The odds ratio for treatment was 0.618, slightly lower than the odds ratio which used the entire follow-up.

Another, more traditional, approach to modeling adherence is to use the indicator of personal adherence of at least 80% as the response in a logistic model. As Table 13 displays, the results fell in line with those discussed already. In this model, most covariates, but not all, yielded significant parameter estimates—the exceptions being flare count, renal impairment, NSAID use, and glucocorticoids.

Table 13. Odds Ratios of Adjusted Adherence Analysis at 1 year

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
Febuxostat (1) vs Allopurinol (0)	0.669	0.642	0.697
Gender: Male (1) vs Female (0)	1.072	1.038	1.107
Age: 45-64 vs 18-44	1.16	1.105	1.218
Age: 65+ vs 18-44	1.168	1.107	1.232

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
Race: Asian vs White	1.057	0.957	1.168
Race: Black vs White	0.855	0.816	0.895
Race: Hispanic vs White	0.782	0.687	0.889
Race: Other vs White	0.695	0.636	0.759
Race: Unknown vs White	0.756	0.729	0.785
Region: Northeast vs Midwest	1.052	1.009	1.098
Region: South vs Midwest	0.735	0.706	0.765
Region: West vs Midwest	0.804	0.769	0.841
Insurance: Medicare vs Commercial	0.848	0.813	0.884
Insurance: Other vs Commercial	0.516	0.474	0.563
Insurance: Unknown vs Commercial	0.892	0.858	0.927
Index Year: 2010 vs 2009	0.594	0.565	0.624
Index Year: 2011 vs 2009	0.544	0.517	0.572
Index Year: 2012 vs 2009	0.453	0.429	0.479
Index Year: 2013-14 vs 2009	0.412	0.388	0.438
BMI: Missing vs Normal	0.938	0.883	0.996
BMI: Obese vs Normal	1.125	1.067	1.186
BMI: Underweight vs Normal	1.019	0.785	1.324
BMI: pre-Obese vs Normal	1.078	1.02	1.14

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	Estimate	95% Confidence Limits	
CKD stage: Stage 4+ vs Stage 1	1.055	0.993	1.122
CKD stage: Stage 3 vs Stage 1	1.073	1.012	1.138
CKD stage: Stage2 vs Stage 1	0.897	0.825	0.975
CKD stage: Missing vs Stage 1	0.871	0.821	0.924
SUA: sUA 6-6.99 vs sUA < 6	1.079	0.996	1.169
SUA: sUA 7-7.99 vs sUA < 6	1.117	1.04	1.199
SUA: sUA 8-8.99 vs sUA < 6	1.183	1.105	1.267
SUA: sUA ≥ 9 vs sUA < 6	0.877	0.826	0.931
SUA: Missing vs sUA < 6	1.243	1.165	1.326
Specialist (1) vs Non-specialist (0)	1.118	1.055	1.185
Tophi (1) vs Non-Tophi (0)	1.17	1.012	1.352
Charlson Index 1 vs 0	0.861	0.82	0.905
Charlson Index 2 vs 0	0.875	0.83	0.921
Charlson Index 3+ vs 0	0.705	0.651	0.763
NSAID use (1) vs No NSAID use (0)	1.078	1.04	1.117
Utilization: 2-3 Meds vs 0-1 Med	1.568	1.489	1.652
Utilization: 4-6 Meds vs 0-1 Med	1.241	1.187	1.297
Utilization: 7-10 Meds vs 0-1 Med	1.391	1.333	1.45
Utilization: 11+ Meds vs 0-1 Med	1.505	1.439	1.575

Unadjusted Persistence

The basic statistics for the unadjusted persistence are displayed in Table 14. For the whole study sample, 34.8% of patients had a gap between prescriptions that qualified as non-persistence. The patients had a rate of 50.9 incidents of non-persistence per 100 person-years, with a 95% confidence interval of [50.3, 51.4]. The patients with an "active flag," which means patients on the medication as of the last data collection point, was 77.5%.

Table 14. Unadjusted Persistence Analysis Results

Person-years	62,767
Non-persistent patients (%)	31,929 (34.8)
Incidence of non-persistence (per 100 person-years)	50.9 [50.3, 51.4]
Active users (%)	70,992 (77.5)
Median Time to non-persistence	1.468 years

The basic statistics for the unadjusted persistence by medication groups are displayed in Table 15. As noted above, Allopurinol patients had a longer follow-up period, which means they stayed on the drug longer. So even though 36% of Allopurinol patients had a gap between prescriptions that qualified as non-persistence, compared to only 27% of Febuxostat patients, the length of time on Allopurinol tended to be longer, and thus persistence was higher overall among Allopurinol patients. This is reflected in the estimates of the incidence of non-persistence. Allopurinol had a rate of 49.7 incidents of non-persistence per 100 person-years, with a 95% confidence interval of [49.2, 50.3], while Febuxostat had a rate of 64.0 non-persistent patients per 100 person-years, with a 95% confidence interval of [61.7,

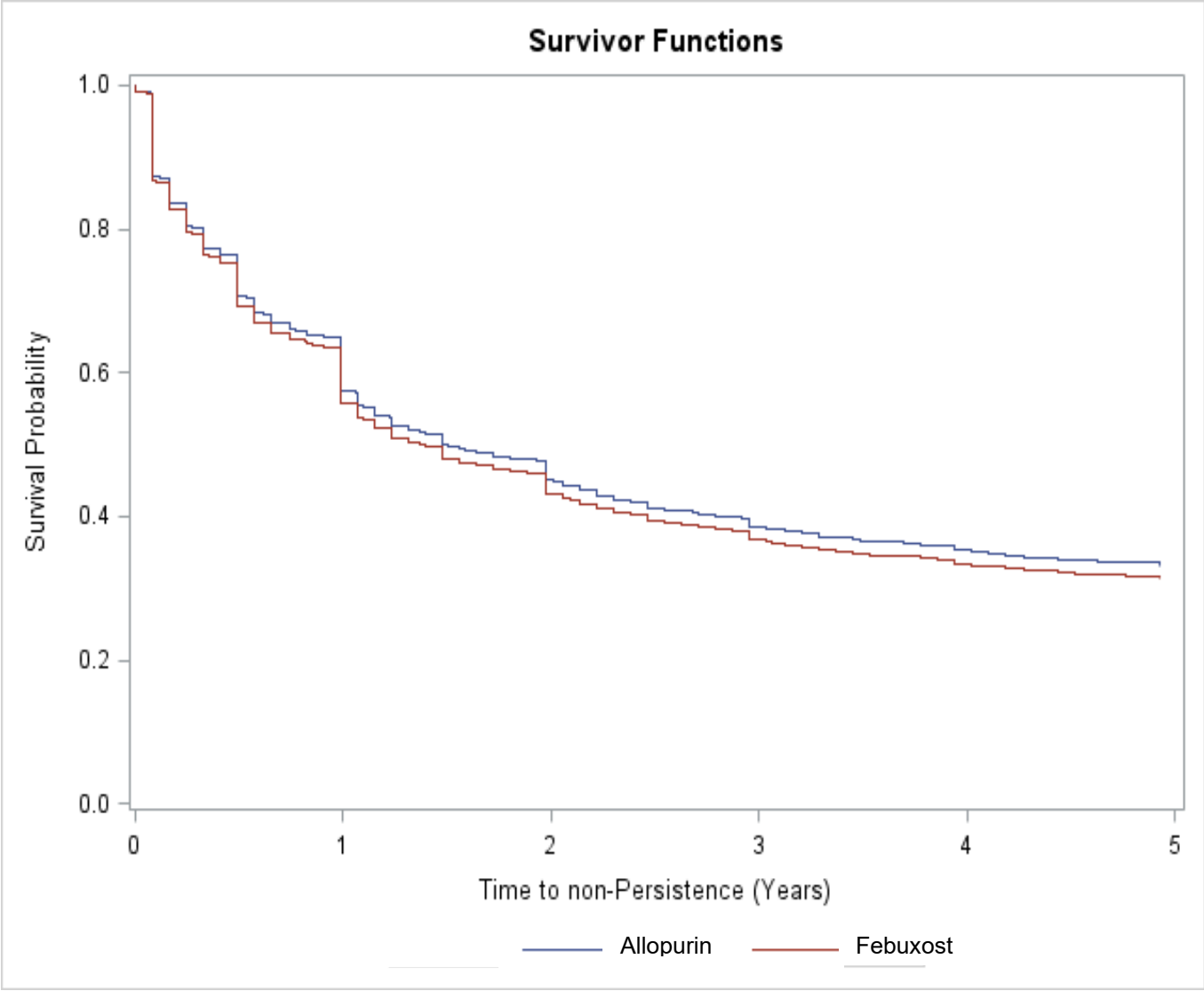
66.2]. The “active flag” was turned on for 81% of the Allopurinol cohort—patients on the medication as of the last data collection point—compared to 55% of the Febuxostat group. However, the overall difference in persistence was minimal, with the hazard ratio (HR) for Febuxostat at 1.05—although the p-value was 0.0074 due to the large sample size.

Table 15. Unadjusted persistence analysis results by medications

	Total N=91,629	**Allopurinol N=79,936**	**Febuxostat N=11,693**
Person-years	62,767	57,809	4,958
Non-persistent patients (%)	31,929 (34.8)	28,758 (36.0)	3,171 (27.1)
Incidence of non-persistence (per 100 person-years)	50.9 [50.3, 51.4]	49.7 [49.2, 50.3]	64.0 [61.7, 66.2]
Active users (%)	70,992 (77.5)	64,567 (80.8)	6,425 (54.9)
Median Time to non-persistence	1.468 years	1.475 years	1.383 years
Hazard ratio			1.05 [1.01, 1.09]

The median time to non-persistence, estimated from the data used to create the Kaplan-Meier survival function in Figure 14, was 17.7 months for Allopurinol and 16.6 months for Febuxostat.

Figure 14. Unadjusted Persistence-- Kaplan-Meier estimate of cumulative Pr (persistence)



Adjusted Persistence

A proportional hazards model or Cox regression was used to model persistence.

A stepwise selection algorithm was used, and covariates with p-values below 0.05 were retained in the model. Table 16 displays covariate p-values for the persistence Cox model when all 19 covariates are included in the model. Seven covariates were eventually

excluded due to p values above 0.05, including Gender, Specialist provider, Tophi, Charlson Index, NSAID, Steroids and Colchicine. There are 2 other covariates with p>0.05, Renal and Flares, but these eventually were included in the final model through the stepwise process. Table 17 displays the same 7 covariates assessed individually at the end of the forward elimination process, where the running Cox model contains the 12 significant covariates. This result also shows p>0.05, although the sizes of the p-values have changed.

Table 16. Stepwise selection process (1): Covariate p-values for the persistence Cox model (All 19 covariates)

Parameter	Wald Chi-Square	Pr > ChiSq
Febuxostat	14.7107	0.0001
Gender	**0.2891**	**0.5908**
Age	62.8104	<.0001
Race	187.0682	<.0001
Region	104.9041	<.0001
Insurance	37.8042	<.0001
Index Year	692.6207	<.0001
BMI	27.1499	<.0001
CKD stage	12.3848	0.0147
SUA	77.5536	<.0001
Specialist	**0.0019**	**0.9651**
Tophi	**0.9902**	**0.3197**
Renal impairment	**2.1410**	**0.1434**
Acute gout arthritis	**5.8154**	**0.0546**
CCI	**6.7174**	**0.0815**
NSAID use	**1.3189**	**0.2508**

Steroid use	**3.1235**	**0.0772**
Colchicine use	**0.0808**	**0.7763**
Heath care utilization	73.4052	<.0001

Table 17. Stepwise selection process (2): Analysis of Effects Eligible for Entry

Effect	**Score Chi-Square**	**Pr > ChiSq**
Gender	0.3060	0.5801
Specialist	0.0896	0.7646
Tophi	1.0234	0.3117
CCI	6.4942	0.0899
NSAID use	1.2985	0.2545
Steroid use	3.1825	0.0744
Colchicine use	0.1338	0.7145

Through the process described above, the stepwise model retained 12 of the 19 available covariates. Table 18 lists the estimated HRs together with their 95% confidence intervals. It should be noted that the overall test for the CKD stage variable yielded a p-value below 0.05, even if none of the categories that make up the variable had a significant HR. The hazard ratio for treatment is 1.07, meaning that after controlling for the covariates in this model, the Febuxostat persistence is significantly lower than that of allopurinol. Another way of stating the finding is that the time to non-persistence is

shorter for the Febuxostat cohort. Applying the HR to the allopurinol raw incidence of non-persistence yields 53.4 non-persistent patients per 100 person-years for Febuxostat, a lower incidence than the unadjusted estimate.

Persistence on ULTs apparently improves with age, as the two older age groups have HRs that are less than one and are decreasing. Among the ethnic groups, Hispanics and Blacks have worse persistence than Caucasians, whose persistence was about the same as that of Asians. The Northeast was the region with the highest persistence, while the South had the lowest. Similarly, to the adherence finding, people on commercial health insurance plans had the highest persistence, compared to those on Medicare and others. Those who started on an ULT in 2009 (reference group) and 2011 had equivalent levels of persistence, better than those who started in 2010, but not as high as the most recent users, people with index years 2012-14. There is some evidence that patients with higher levels of uric acid tend to have higher persistence. Looking at the health utilization measure, better persistence to ULTs is found among patients taking more medications.

Table 18. Hazard Ratios of Adjusted Persistence Analysis– Cox regression results

Analysis of Maximum Likelihood Estimates					
Parameter		p-value	Hazard Ratio	95% Hazard Ratio Conf Limits	
Medication	Febuxostat (1) vs Allopurinol (0)	0.0002	1.074	1.034	1.115

Analysis of Maximum Likelihood Estimates					
Parameter		p-value	Hazard Ratio	95% Hazard Ratio Conf Limits	
Age	45-64 vs 18-44	<.0001	0.893	0.859	0.929
	65+ vs 18-44	<.0001	0.841	0.806	0.879
Race	Asian vs White	0.4774	1.029	0.951	1.114
	Black vs White	<.0001	1.107	1.067	1.149
	Hispanic vs White	0.0268	1.120	1.013	1.237
	Other vs White	<.0001	0.710	0.652	0.772
	Unknown vs White	<.0001	0.868	0.841	0.896
Region	North East vs Midwest	<.0001	0.910	0.879	0.942
	South vs Midwest	0.0013	1.055	1.021	1.090
	West vs Midwest	0.1267	1.029	0.992	1.066
Insurance	Medicare vs Commercial	<.0001	1.108	1.071	1.146
	Other vs Commercial	0.0753	1.069	0.993	1.150
	Unknown vs Commercial	<.0001	1.088	1.054	1.122
Index year	2010 vs 2009	<.0001	1.148	1.108	1.189
	2011 vs 2009	0.9980	1.000	0.962	1.039
	2012 vs 2009	<.0001	0.817	0.782	0.854
	2013-14 vs 2009	<.0001	0.496	0.470	0.525
BMI	Missing vs Normal	<.0001	1.108	1.053	1.166
	Obese vs Normal	0.2030	1.030	0.984	1.078
	Underweight vs Normal	0.0829	0.794	0.611	1.030
	pre-Obese vs Normal	0.1024	1.041	0.992	1.092

Analysis of Maximum Likelihood Estimates					
Parameter		p-value	Hazard Ratio	95% Hazard Ratio Conf Limits	
CKD stage	Stage 4+ vs Stage 1	0.0992	1.060	0.989	1.135
	Stage 3 vs Stage 1	0.1458	1.038	0.987	1.091
	Stage 2 vs Stage 1	0.9959	1.000	0.953	1.049
	Missing vs Stage 1	0.5513	0.985	0.939	1.034
sUA	sUA 6-6.99 vs sUA < 6	0.0996	0.946	0.885	1.011
	sUA 7-7.99 vs sUA < 6	0.0094	0.925	0.872	0.981
	sUA 8-8.99 vs sUA < 6	0.0052	0.923	0.872	0.976
	sUA ≥ 9 vs sUA < 6	0.0969	0.956	0.908	1.008
	Missing vs sUA < 6	0.0210	1.059	1.009	1.111
Diagnosis of renal impairment	Renal impairment (1) vs Non-Renal impairment (0)	<.0001	1.094	1.049	1.142
Number of diagnoses of acute gout arthritis	1 vs 0	0.0056	0.950	0.916	0.985
	2-3 vs 0	0.8765	1.021	0.782	1.335
Heath care utilization	2-3 Meds vs 0-1 Med	<.0001	0.903	0.871	0.937
	4-6 Meds vs 0-1 Med	<.0001	0.876	0.846	0.907
	7-10 Meds vs 0-1 Med	<.0001	0.850	0.819	0.882
	11+ Meds vs 0-1 Med	<.0001	0.867	0.832	0.904

Subgroup Analysis

In addition to analyzing the entire study population, I conducted two sub-group analyses. Two subgroups of the full study cohort were compared in terms of their unadjusted adherence and persistence, as well as their adjusted adherence: (i) patients who had tophi or at least one flare at baseline, and (ii) patients who were prescribed NSAIDs, steroids or colchicine at baseline. These factors are included as covariates in the adjusted analysis, because it is considered meaningful to investigate the patient behavior of the population who might have higher medical needs and those who might have more treatment induced flares. The severity of disease status and importance of prophylaxis might have major impacts on medication adherence based on the results from previous studies.

Baseline flares or tophi

About 13.4% of all study patients had either tophi or at least one flare during the 6-month baseline. The basic statistics comparing the unadjusted adherence between drug treatments were displayed in Table 18, while the unadjusted persistence was shown in Table 19. Within this subgroup, allopurinol patients obtained a larger supply of drug and were more adherent than Febuxostat patients. The two treatment groups had very similar measurements of uric acid at baseline, both with a mean of 8.7.

The same basic adherence statistics appear at the bottom of Table 19 for the case when the follow-up is limited to the first year after the index date. The overall rates of adherence were higher than over the full follow-up period, while the differences between the two treatment groups were comparable. Modeling adherence with the covariates included as in the full population—but omitting the covariates which defined the subgroup—yielded an odds ratio for treatment of 0.676, with $p<0.0001$, meaning that the adjusted Febuxostat adherence was statistically significantly lower than that of Allopurinol. Applying the formula to convert the odds ratio to a relative risk yielded 43.8% as the average adherence for Febuxostat, a slightly lower adherence than the unadjusted estimate in Table 19. A logistic regression using the indicator of personal adherence of at least 80% as the dependent variable yielded very similar results (OR=0.715).

As in the full cohort, a larger percentage (34%) of Allopurinol patients in the subgroup had a gap between prescriptions that qualified as non-persistence, compared to Febuxostat patients (27%), but time on Allopurinol tended to be longer, and thus persistence was higher overall among Allopurinol patients. This is reflected in Table 19's

higher estimate of incidence of non-persistence among Febuxostat patients—the raw hazard ratio of 1.17 achieved significance with a p-value of 0.001.

Table 19. Unadjusted Adherence among patients with 1+ Flares or Tophi (N=12,533)

	Allopurinol **N=10,647**	Febuxostat **N=1,886**
Supply: mean, median (SD) days	413, 276 (417)	242, 114 (313)
Follow-up: mean (SD) years	2.1 (1.4)	1.5 (1.3)
Individual Adherence ≥ 80%	4,143 (38.9%)	670 (35.5%)
Adherence	**53.6%**	**44.6 %**
1-year only		
Individual Adherence ≥ 80%	5,951 (55.9%)	896 (47.5%)
Adherence	**66.8%**	**56.4 %**

Table 20. Unadjusted Persistence among patients with 1+ Flares or Tophi (N=12,533)

	Allopurinol **N=10,647**	Febuxostat **N=1,886**
Person-years	8,580	868
Non-persistent patients (%)	**3,642 (34.2)**	**511 (27.1)**
Incidence of non-persistence (per 100 person-years)	42.4 [41.1, 43.8]	58.9 [53.9, 64.2]
Active users (%)	8,269 (77.7)	966 (51.2)
Median Time to non-persistence	1.963 years	1.458 years
Hazard ratio		**1.17 [1.06, 1.28]**

Baseline NSAIDs, steroids or colchicine

About 48.9% of all study patients were prescribed either NSAIDs, steroids or colchicine during the 6-month baseline. The basic statistics comparing the unadjusted adherence were displayed in Table 21, while the unadjusted persistence was shown in Table 22. Again, Allopurinol patients obtained a larger supply of drug and were more adherent than Febuxostat patients. The two treatment groups had very similar measurements of uric acid at baseline, with means of 8.5 in the Allopurinol group and 8.4 in the Febuxostat group.

The same basic adherence statistics appear at the bottom of Table 21 for the case when the follow-up is limited to the first year after the index date. The overall rates of adherence were higher, and the difference between the two treatment groups was higher than over the entire follow-up period. Modeling adherence with the covariates included

as in the full population—but omitting the covariates which defined the subgroup—yielded an odds ratio for treatment of 0.672, with p<0.0001, meaning that the adjusted Febuxostat adherence was significantly lower than that for the Allopurinol group A logistic regression using the indicator of personal adherence of at least 80% as the dependent variable yielded very similar results (OR=0.680).

From the results in Table 22, more Allopurinol patients were non-persistent over the follow-up than Febuxostat patients (37% vs. 29%), but the incidence of non-persistence was higher among Febuxostat patients—the raw hazard ratio of 1.15 achieved significance with a p-value below 0.001.

Table 21. Unadjusted Adherence among patients with NSAIDs, Steroids or Colchicine (N=44,849)

	Allopurinol **N=37,468**	Febuxostat **N=7,381**
Supply: mean, median (SD) days	434, 300 (444)	249, 115 (323)
Follow-up: mean (SD) years	2.3 (1.4)	1.6 (1.3)
Individual Adherence ≥ 80%	13,665 (36.5%)	2,438 (33.0%)
Adherence	**51.8%**	**42.4 %**
1-year only		
Individual Adherence ≥ 80%	21,108 (56.3%)	3,409 (46.2%)
Adherence	**66.0%**	**54.7 %**

Table 22. Unadjusted Persistence among patients with NSAIDs, Steroids or Colchicine (N=44,849)

	Allopurinol **N=37,468**	Febuxostat **N=7,381**
Person-years	30,515	3,384
Non-persistent patients (%)	**13,784 (36.8)**	**2,153 (29.2)**
Incidence of non-persistence (per 100 person-years)	45.2 [44.4, 45.9]	63.6 [61.0, 66.4]
Active users (%)	29,343 (78.3)	3,812 (51.7)
Median Time to non-persistence	1.766 years	1.225 years
Hazard ratio		**1.15 [1.10, 1.21]**

Chapter 5 Discussion/Conclusions

Discussion of findings from the Adherence analysis

This study provided a more comprehensive view about the adherence of patients with gout because the total sample size of this study is 91,629 patients, which is much larger than those of previous studies which analyzed medication adherence among patients with gout. In addition, the distributions of demographics in the database used for this study are generally similar to that of the overall U.S. population whereas some previous studies focused on specific subpopulations.

Baseline characteristics of study population are similar with the previous studies. At the baseline, those prescribed Febuxostat were more obese patients, had higher numbers in the latter stages of CKD, had fewer patients with missing uric acid test results, and more who received their first prescription from a specialist. Considering that the careful dose adjustment is required to prescribe Allopurinol for higher CKD patients (Febuxostat is considered to have relatively less burden for CKD patients because of the mechanism), the differences in CKD between the 2 groups are reasonable. Also, the findings are consistent with the previous findings that specialists seek the newly available treatment with the branded medicine. Also “unlearning” might be related in terms of the practice changes which may be required of physicians (especially non-specialists). Gupta et al pointed out that physicians face various struggles in order to successfully change practice when a change is introduced (e.g. guideline changes) in their qualitative study of the practices of the general physicians. They mentioned that the guideline change and new information makes for uncertainty and discomfort which may inhibit behavior change among physicians. [44]

In the unadjusted adherence analysis with the total study population, 32.0% of patients achieved a personal adherence of at least 80% and the overall average adherence was 46.4%. These numbers are considered to be aligned with those which were reported by previous studies. In three previous studies, 36.8 % (Briesacher et al. 2008), 36% (Solomon et al. 2008) and 44% (Halpern et al. 2009) of patients achieved a personal adherence of at least 80%.[30] [32] [33] As confirmed in Chapter 2, the adherence among gout patients has been significantly low, compared with other chronic diseases. For example, in the study by Briesacher et al. (2008), 72.3 % of hypertension patients achieved a personal adherence of at least 80% whereas 36.8% of gout patients did. [30] This finding suggests that there is a large room to improve the adherence of patients with gout.

In the unadjusted analysis by medication groups, 32.2 % of patients with Allopurinol and 30.4 % of those with Febuxostat achieved a personal adherence of at least 80%. According to Schulman K, the monthly cost for Allopurinol was 5 USD whereas the cost for Febuxostat was 155 USD. [45] Considering the drug price difference between Allopurinol and Febuxostat, this difference in personal adherence could well be due to the price difference as suggested by market research which has found generally higher patient co-pays for Febuxostat. This may help explain the lower adherence among patients on Febuxostat. Because of the data limitations of this database, it is difficult to reach conclusions, but the difference in adherence may also be related to SES factors and insurance status.

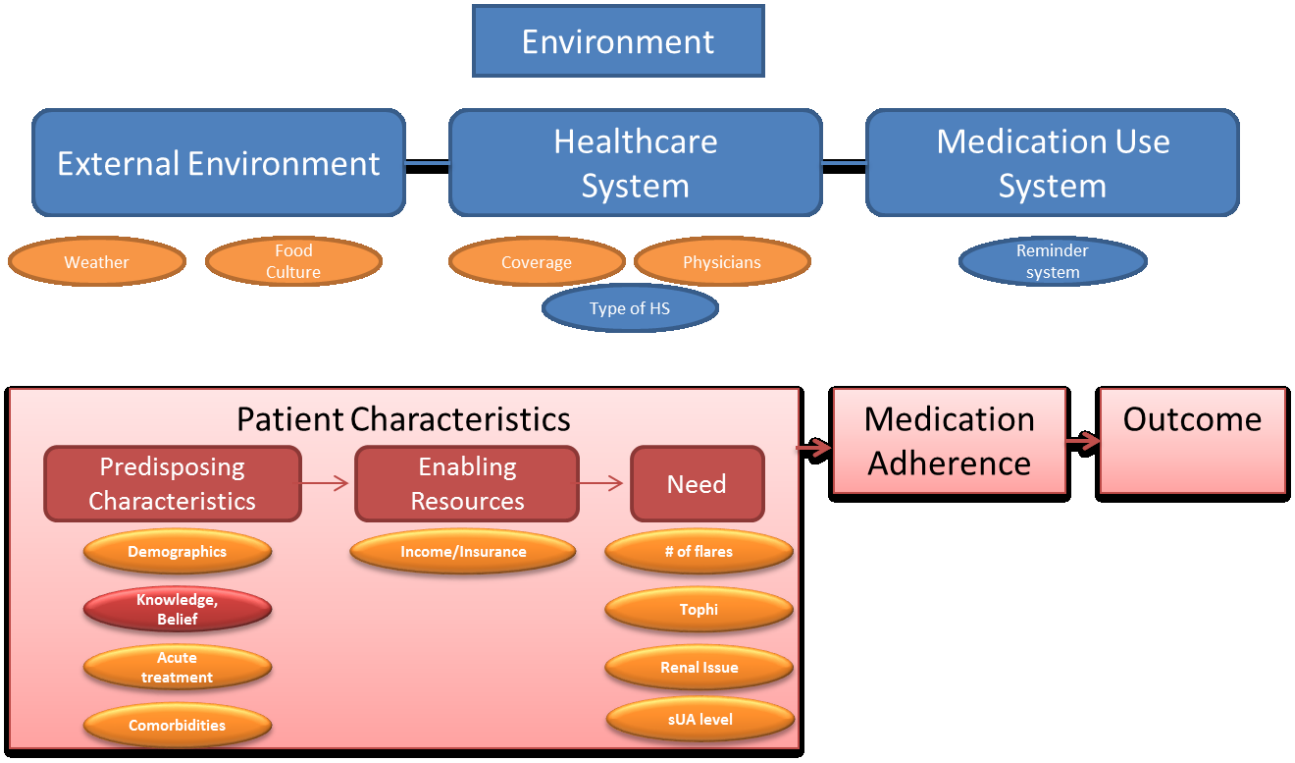
In the adjusted analysis, one of biggest factors associated with adherence was the medication, with an odds ratio which was 0.654. The Febuxostat adherence was significantly lower than that of Allopurinol after controlling for the covariates in this model. The reasons why medication had a significant impact were considered to be: 1) Financial burden (As described above, there was a

substantial difference in cost between Allopurinol and Febuxostat.), and 2) Possibly better effectiveness (Considering the mechanism of ULT induced flare, the more effective treatment may have higher risk of further attack which might have made patients stop taking medications. The number of flares at baseline were controlled, but the flares that occurred in follow-up were not controlled.) More details about possible interventions to improve adherence will be discussed in the following section. In addition, a concern regarding cardiovascular risk related to Febuxostat was mentioned by the FDA when it was launched in the US market. This also might have impacted patients' behaviors.

Other than medication, several factors were identified as factors associated with gout medication adherence. Figure 15 is the Conceptual Framework for Gout Medication Adherence which was developed based on the review of previous studies. The elements identified as important in this study are highlighted in the Figure below.

- Some elements (weather, food culture) were not included in the database, but are considered to be related to some of the other factors in this analysis (region, race).
- Some elements in the conceptual framework (type of healthcare system, reminder system or not, individual belief/knowledge, etc.) could not be studied because they are not available in the database.
- Some elements in the conceptual framework (acute treatments, number of gout flares, etc.) were studied, but a clear relationship with adherence to gout medications could not be determined. (The results of the statistical analysis were significant because the sample size was large, however either the results were not strong compared with other elements, and/or the results were not consistent.)

Figure 15. Conceptual Framework for Gout Medication Adherence with highlights based on the adjusted adherence analysis



Discussion of findings from the Persistence analysis

In the unadjusted analysis, 31929 patients (34.8% of all patients) had a gap between prescriptions which is considered as non-persistence. The patients had a rate of 50.9 incidents of non-persistence per 100 person-years, with a 95% confidence interval of [50.3, 51.4]. The patients with an "active flag," which means patients were on the medication as of the last data collection point, was 77.5%. Median time to non-persistence in the unadjusted analysis was 1.468 years. Compared with the previous study by Solomon et al, [32] median time was a little bit longer, but the overall trends were similar.

In the adjusted analysis, as in the case with the adherence analysis above, the type of medication had a significant impact on persistence. Patients on Febuxostat had a significantly lower persistence than those on allopurinol. Other factors also had similar trends with the adherence analysis described above. Persistence apparently improves with age. Among the ethnic groups, Hispanics and Blacks have worse persistence than Caucasians, whose persistence was about the same as that of Asians. The Northeast was the region with the highest persistence, while the South had the lowest. Patients with commercial health insurance plans had the highest persistence, compared to those with Medicare and other types of insurance.

Discussion of findings from subgroup analysis

In addition to analyzing the entire study population, two sub-group analyses were conducted for the following: (i) patients who had tophi or at least one flare at baseline, and (ii) patients who were prescribed NSAIDs, steroids or colchicine at baseline. These factors were included as covariates in the adjusted analysis, but these subgroup analyses were conducted to investigate the

patient behavior of the populations who might have higher medical needs and those who might have more treatment induced flares. Although there was a hypothesis that these factors might have impacts on patient behaviors, significant differences from the results for the entire study population were not found.

Conclusions and Implications for Interventions to improve Adherence and Persistence

Conclusions

The difference between the types of medication (Febuxostat or Allopurinol) used for ULT was one of the factors associated with patient adherence to chronic gout medication from the standpoint of statistical (although not necessarily clinical) significance. As discussed above, the following reasons may be considered in explaining this trend.

1) The cost difference between Febuxostat and Allopurinol

   As mentioned above, there is a significant price difference between Febuxostat and Allopurinol, as suggested by market research which has found generally higher patient co-pays for Febuxostat. This may explain the lower adherence among patients on Febuxostat.

2) Better effectiveness of Febuxostat on lowering sUA

   Considering the mechanism of ULT induced flare, better effectiveness may lead to the higher risk of further attack. [35] (Numbers of flares at baseline were controlled in this study, but the flares occurred during follow-up were not controlled.) As a result, this

might make patients stop taking medications. [46] As Odera et al. have pointed out, prophylaxis to prevent further attack is generally not enough and physicians do not follow the guideline which recommends the prophylaxis. [36]

However, because switching between medications cannot be analyzed in this study, further research to consider patients' behavior after switching medicines is needed to reach better conclusions regarding the impact of medications on adherence.

Other than type of medication, the analysis identified the following factors which are associated with gout medication adherence. The findings from this study are consistent with those which were reported in the previous studies. The factors in () are associated with higher adherence.

- Gender (Female > Male)
- Race (Asian > Caucasian; > Black; > Hispanic)
- Region (Northeast > Midwest; > West; > South)
- Insurance (Commercial > Medicare)
- BMI (Obese > Pre-obese; > Normal; > Underweight)
- CKD stage (Stage 2 > Stage 3; > Stage 1; > Stage 4)
- Specialist vs. Non-specialist provider classifications (Specialist > Non-specialist)
- Diagnosis of gout tophi (With tophi > Without tophi)
- Diagnosis of renal impairment
- Serum uric acid measurements (Higher sUA > Lower sUA)
- Number of diagnoses of acute gout arthritis (gout flares, separated from each other by at least 30 days) (1 flare > 0 flare; > 2-3 flares)

- Comorbidities (Quantified with the Charlson Comorbidity Index (CCI)) (3+ > 2; > 1; > 0)
- Use of NSAIDs (With NSAID > Without NSAID)
- Use of colchicines (With Colchicines > Without Colchicines)
- Use of glucocorticoids (With steroids > Without steroids)
- Heath care utilization (number of different types of medications used during baseline) (11+ > 7-10; > 4-6; > 2-3; > 0-1)

Possible interventions to improve Adherence and Persistence

Based on the analysis results and the conceptual framework derived from the results of previous studies, several interventions can be considered to improve the adherence and persistence to gout medications.

Cost burden mitigation

In this study, the analysis results showed that the type of insurance is associated with both adherence and persistence. In both analyses, patients with commercial insurance had better adherence and persistence compared to those with Medicare, other types of insurance and unknown insurance status. Because this database does not have other items related to financial matters, it is difficult to draw conclusions, but the implication is that the cost burden is one of the factors which have a negative impact on adherence.

For those who cannot afford gout medication due to financial reasons, there are several support programs. However, only the population with significantly low SES can be eligible for

these programs. Most patients who can access a minimum level of health services, but not higher quality services, cannot utilize these support programs. [47]

In addressing the price difference between Febuxostat and Allopurinol, there are some programs to support the cost of Febuxostat from Takeda, a pharmaceutical company who is manufacturing Febuxostat. But all programs sponsored by them are only available for the first 90 days. Considering that the drop in adherence happened at 90 days, their programs might not be enough to keep patients on medications. As a possible intervention to mitigate the cost burden of gout medications (especially brand-generic price differences), the development of expanded (beyond 90 days) coupon programs should be considered with the support from a brand medicine manufacturer. In the mid-/long- range, after the Febuxostat patent expiration which will occur in a few years, the price differences between Febuxostat and Allopurinol will be decreased.

In addition, some may argue that insurance companies tend to underestimate the threat of gout and consider gout as just a temporary inflammatory attack creating pain which can be simply controlled by NSAIDs. However, as discussed in Chapter 2, the negative impact of gout on other complications (e.g. CKD, DM, CV risk) in the long-term suggest that gout should be treated as a chronic disease with adequate treatments in the long-term, not just as a single incident. Encouraging the insurance companies to reconsider their recommended treatment plan/coverage also can be a possible way to mitigate the financial burden of gout management.

Patient education / Reminder systems

To improve the adherence to gout medications, one of the most important things is to make patients fully aware of the disease and treatments for how to control the disease. However, gout

is known as a disease which patients don't understand well. Spencer et al. pointed out the lack of knowledge and understanding of the causes and consequences of gout and that it can be treated effectively by lifestyle change and use of urate lowering therapy (ULT). They also reported that many patients viewed gout as self-inflicted or part of ageing and only focused on managing acute attacks, rather than treating the underlying cause. [48] Coburn et al. reported that the majority of gout patients didn't understand the treatment goals. Of the 62 percent of patients who answered their questionnaire, only 14 percent knew a target sUA and nearly 80 percent expressed a general lack of knowledge about their treatment goals [49].

In this study, because of the data limitations of the retrospective analysis of secondary data, the factors which are directly related to patient education and awareness are not included in the analysis. However, several factors which might be indirectly related (Age, Gender, Race, Region, seeing specialists/non-specialists and Utilization) imply that the patients' backgrounds/knowledge of disease might be related to the adherence.

In order to find solutions to patients' disease awareness issues, Rees et al. conducted a study with a nurse-delivered intervention that included education, individualized lifestyle advice and appropriate ULT and confirmed that the intervention could successfully achieve the recommended treatment target in more than 90% of patients. [50] Also, several nonprofit organizations provide patient education tools targeting patients directly (mostly available through the websites) and indirectly via healthcare professionals. Through the collaboration with these organizations, a targeted patient education campaign focusing on vulnerable populations (based on the identified factors from this study) might be effective in improving patient adherence efficiently.

Related to patient education, a reminder system is also important to consider as a possible solution to how to improve patient behavior regarding adherence, as identified through the analysis based on the conceptual framework discussed above. With the current technology, there are several methods to remind patients to follow the chronic disease management. Especially, the reminder systems using apps available on smartphones are widely available. Some apps have several functions, not only simpler reminders but also disease education and life style advice. However, compared with other therapeutic areas like Disease Management, there are very few apps focusing on gout management. Nguyen et al. concluded in their study of 57 identified apps, that only one app exists that includes all recommendations to facilitate patient self-management of gout. [51] Their manuscript was published 2 years ago in 2016. But the situation since then has not changed very much. As one of the interventions to improve gout adherence, the development of new apps might be worth considering.

Physician education

To improve the patients' knowledge about gout management, physician education is considered to be critical.

As discussed in Chapter 2, Odera et al. pointed out that there is room to improve the physicians' treatment compliance with ACR guidelines among both primary care physicians (PCPs) and rheumatologists. Although both specialists and PCPs have room to improve, they reported that PCPs are less compliant with the treatment guidelines than rheumatologists. [36] As mentioned previously regarding the lack of knowledge on the patients' side, Doherty et al. reported that only a minority of patients with gout receive adequate advice and treatment from

physicians. They also discussed that physicians often focus on managing acute attacks rather than viewing gout as a chronic disease because of the lack of adequate physician education. [52]

Also as discussed, "unlearning" may be necessary for the practice change of physicians (especially non-specialists), and they may face various struggles in order to successfully change practice when a change is introduced (e.g., guideline change, new innovation). [44]

This study found that there is a positive association with adherence if the physician is a specialist (rheumatologist/ nephrologist). This finding may suggest that physicians' knowledge about gout management might be related to adherence. Based on this supposition, physician education, especially focusing on GP/Family medicine physicians, might be an effective intervention to improve patients' adherence to gout treatments.

Strengths and Limitations of this Study

As mentioned above, this study is the first comprehensive study which examined the medication adherence to Febuxostat, a new medication option launched in 2009 in the large U.S. population. As a benefit of the large EMR database, the sample size of this study is much larger than those of previous investigations and the data cover a broader range of regions and populations compared with the previous studies. The findings from this comprehensive study strengthen the findings from previous studies, contribute to clarifying the causes of low adherence to chronic gout medications (which may create repeated flares leading to lower HRQoL and higher medical costs), and have implications for solutions to improve the current low adherence to gout medications.

At the same time that there are benefits of the large EMR database, there are also several limitations. Because the database is completely de-identified following the HIPPA regulation, some information is not available in the database and individual patients cannot be linked with other databases to obtain additional information. Also, there are missing values, especially in the laboratory and prescription data. Although significant differences in terms of missing data among groups was not found in this study, concerns remain. This is one of the big challenges in using existing databases for analysis.

As another limitation of the database used in this study, adherence cannot be measured with the tools confirming the actual intake of medication (e.g. the usage of special bottles examined in the data collection). Also, the EMR database contains prescription data, but not the filling data. It is reported that about a third of patients fail to fill their first-time prescriptions [53]. Also, it is not possible to detect the relationship between the prescription and actual filling of the prescription in the analysis with this EMR database. Therefore, it is important to admit the possibility that there exist unadjusted confounders outside this database. However, considering the MPR calculation methods that were used (the days supply of medication dispensed (excluding the last refill) divided by the number of days between the first and last prescription refill) and that the eligible patients in this study came back to their clinics for follow-ups and received ≥2 prescriptions, it may still be reasonable to assume that the MPR can detect the adherence to chronic medications using prescription data.

Additionally, there is no detailed dosage information regarding prescriptions in this database. Therefore, it is not possible to explore changes in the prescribed dosages of medications. Also, due to the limitations of the dataset, switching between medications could not be analyzed.

Suggestions for Future Studies

Although this study clarified some possible issues of patient adherence to gout medication with a large sample size which can represent the entire U.S. population, there are many data limitations because of the database characteristics.

Additional studies to clarify the relationships between the many possible factors associated with gout medication adherence are suggested, especially related to: 1) the financial burden, 2) patient education, and 3) physician education. It would be ideal to develop the intervention plans to overcome these issues and measure the effects of these interventions.

Conflicts of Interests

I, Aki Shiozawa, was a full-time employee of Takeda Pharmaceuticals International, Inc. (Deerfield, IL), a manufacturer of Febuxostat in the US, Canada and Mexico when I conducted the analysis. Takeda permitted me to access the GE Centricity Electronic Medical Record (EMR) database and to conduct this research for my dissertation.

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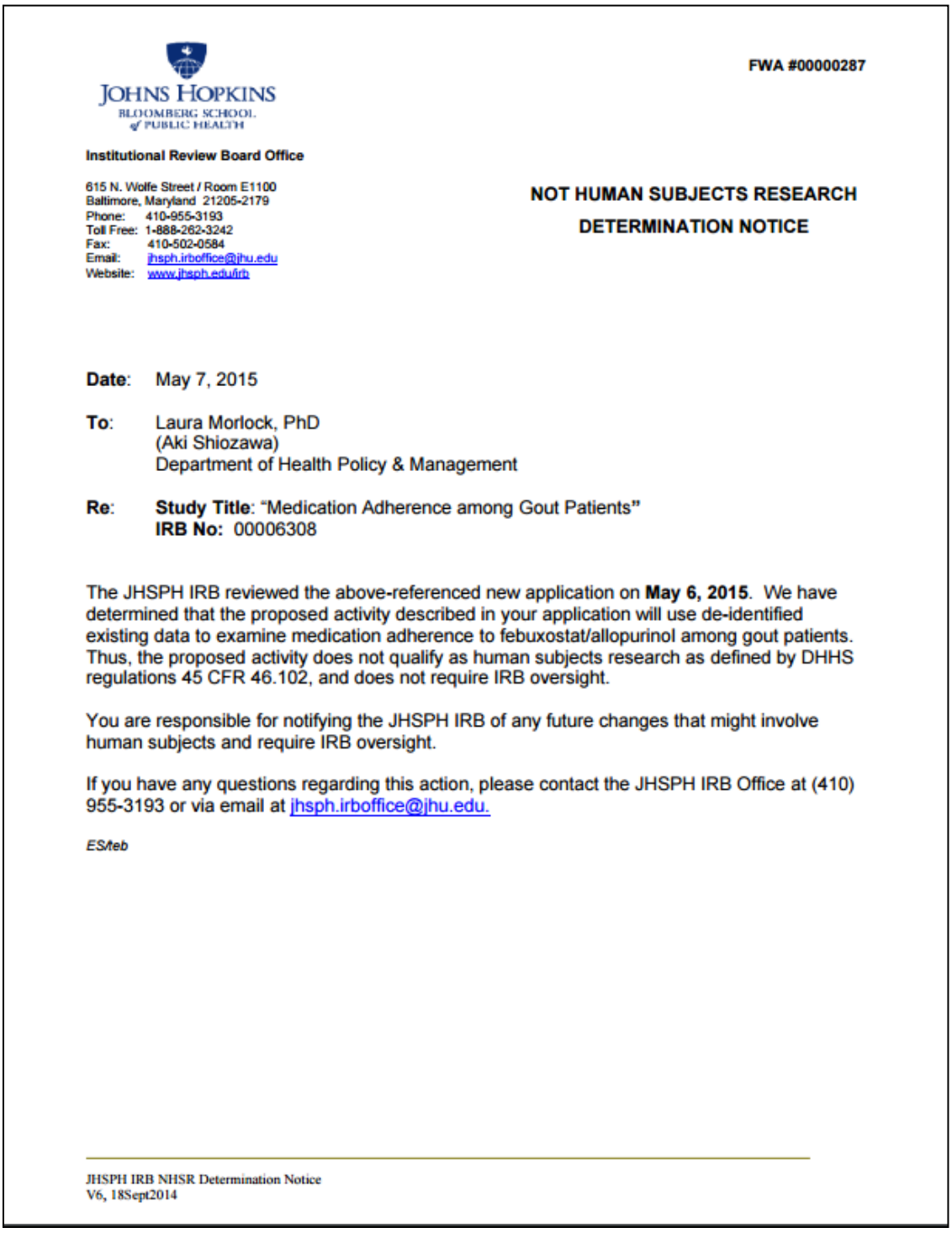
Appendix A: IRB Determination Notice



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NOT HUMAN SUBJECTS RESEARCH
DETERMINATION NOTICE

Date: May 7, 2015

To: Laura Morlock, PhD
(Aki Shiozawa)
Department of Health Policy & Management

Re: **Study Title**: "Medication Adherence among Gout Patients"
IRB No: 00006308

The JHSPH IRB reviewed the above-referenced new application on **May 6, 2015**. We have determined that the proposed activity described in your application will use de-identified existing data to examine medication adherence to febuxostat/allopurinol among gout patients. Thus, the proposed activity does not qualify as human subjects research as defined by DHHS regulations 45 CFR 46.102, and does not require IRB oversight.

You are responsible for notifying the JHSPH IRB of any future changes that might involve human subjects and require IRB oversight.

If you have any questions regarding this action, please contact the JHSPH IRB Office at (410) 955-3193 or via email at jhsph.irboffice@jhu.edu.

ES/teb

JHSPH IRB NHSR Determination Notice
V6, 18Sept2014

Appendix B: Summary of Literature Review

Author	Data Source	Number of patients	Study population	Outcome	Covariates	MPR>80%	Findings	Note
Briesacher et al. (2008)	Health care claims data	9715	US population >18 year old patients who had diagnosis of gout during study period 2001-2004	MPR	age, sex, geographic residence, history of drug, type of health plan, and a comorbidity score calculated by using the Hierarchical Condition Categories risk adjuster	36.80%	MPRs increased with increasing **comorbidities** and **ages**. History of drug use, health plan, the subject's geographic area of residence, or Sex did not influence adherence.	Comparison of drug adherence among patients with 7 different conditions. No Lab data
Riedel et al. (2004)	Administrative claims database	5597	US population Gout patients who filed at least 2 allopurinol prescriptions. Subjects identified from 1997-1998	MPR (They don't use the name of MPR, but concept is same. "Compliance rate = days supply from 1st prescription filled / [fill date of 2nd prescription filled – fill date of 1st prescription filled")	sex, age, prescription filled, comoribidity (diabetes, hypertension, Renal failure, Obesity, RA, Depression, OA)	18%	**Sex** (female has better compliance), **Age**, **Diabetes** and **hypertension** are associated with increased compliance.	No Lab data
Sarawate et al. (2006)	A southeastern US health plan database (regional DB)	2405	US population >18 year old gout patients taking allopurinol. Data from 1999-2002	MPR	age, sex, preindex comorbidities, newly or previously diagnosed gout, and gout flare before postindex serum urate testing	26%	Patients with a **gout flare** before postindex serum urate testing were 50% less likely to be compliant. Patients with baseline **hypertension** were 44% more likely to be compliant.	No Lab data
Harrold et al. (2008)	The healthcare deliversy system database of two systems are located in the Northeast and Rocky Mountain regions of the USA	4166	US population >18 year old gout patients taking allopurinol. Data from 2000-2006	MPR	demographic age, sex, health care utilization (visits to providers for gout both prior to and after ULD initiation, all provider visits prior to ULD initiation, and number of hospitalizations prior to ULD initiation), specific comorbidities, medications.	44%	Predictors of poor adherence included younger **age**, fewer **comorbid conditions** , no **provider visits** for gout prior to urate-lowering drug initiation , and **use of NSAID** prior to urate-lowering drug initiation	No Lab data
Solomon et al. (2008)	US Medicare system and a pharmacy benefit for older low-income adults in the state of Pennsylvania, the Pharmacy Assistance Contract for the Elderly (PACE).	9823	US population >65 year old patients enrolled in pharmacy benefit program	percentage of days covered (PDC),a measure almost identical to the Medication Possession Ratio (MPR) Calculated as the days with available UALT divided by the total number of days of follow-up	age, gender, race), medical care intensity (number of physician visits, number of different medications used, number of acute care hospitalisations), comorbid conditions, gout specific factors (the number of acute gout arthritis diagnoses; a diagnoses of nephrolithiasis; a diagnosis of tophi; a diagnosis of interstitial nephritis; the use of selective or non-selective NSAID, colchicine, or glucocorticoids and uric acid measurements), and physician characteristics (sepcialist or not)	36%	Predictors of poor adherence included younger **age**, **African–American race** and prescription from **non-specialist physicians.**	No Lab data
Halpern et al. (2009)	Administrative claims database	10,070	US population >18 year old gout patients	MPR	sUA	44%	Compliance was positively associated with favorable sUA in unadjusted comparisons.	Lab data (sUA only) - no other covariates
Zandman-Goddard et al. (2013)	National Healthcare Service database	7644	Israel population >25 years patients with the diagnosis of gout treated with allopurinol identified over a 7-year period (2002-2009)	Proportion of days covered (PDC), a measure almost identical to the MPR	age, sex, marital status, place of residency, years of stay in Israel, socio-economic level, chronic conditions, BMI, smoking	17%	**Women aged** 45-64 years, **non-married** individuals, those of **low socioeconomic status** and those with **lower BMI** were more likely to discontinue therapy. Better compliance was achieved among those with **comorbidities.**	

Curriculum Vitae

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EDUCATION

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Doctor of Public Health in Health Care Management and Leadership Department of Health Policy and Management Bloomberg School of Public Health	2011 – Present
Master of Public Health Bloomberg School of Public Health	2007 – 2009
Master of Business Administration Carey Business School	2007 – 2009
Certificate in Quality, Patient Safety, and Outcomes Research	2015
Certificate in Public Health Informatics	2014
Certificate in Public Health Economics	2009

Keio University Tokyo, Japan

Bachelor of Arts	1996- 2000

Work Experience

Astellas Pharma, Inc. Northbrook IL USA 2018 – Present

Director, Health Economics & Outcome Research (HEOR)	2018 – Present

Takeda Pharmaceuticals Deerfield IL USA/Osaka Japan 2009 – 2018

Associate Director, CNS/Immunology, Global Outcome Research	2015 – 2018
Senior Manager, Immunology, Global Outcome Research	2012 – 2015
Manager, R&D Finance/Portfolio Management, Chief Medical & Scientific Officer Office	2012
Manager, Strategic Planning, Strategic Product Planning Department	2009 – 2012

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Sales Representative and Safety Advisor, Cordis Cardiology 2005 – 2007
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PwC Consulting Tokyo Japan 2000 – 2003
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Research/Teaching Experience

Kyoto University Kyoto Japan 2017 – Present
Adjunct Lecturer, Department of Healthcare Epidemiology, School of Public Health 2017 – Present
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MANUSCRIPTS

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ABSTRACTS

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CERTIFICATIONS & QUALIFICATIONS

- Certified Project Management Professional (PMP) by Project Management Institute (PMI)
- Certified in Public Health (CPH) by The National Board of Public Health Examiners (NBPHE)
- Certificate in Quality, Patient Safety, and Outcomes Research (2015, Johns Hopkins School of Public Health)
- Certificate in Public Health Informatics (2014, Johns Hopkins School of Public Health)
- Certificate in Public Health Economics (2009, Johns Hopkins School of Public Health)
- SAP Certified Application Consultant (Financial Accounting/Cost Accounting)